CANCER RESEARCH

VOLUME 8
NUMBER 1
JANUARY, 1948

A MONTHLY JOURNAL
REPORTING CANCER RESEARCH

CONTENTS

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1832-1947

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THE OFFICIAL ORGAN OF THE
AMERICAN ASSOCIATION FOR CANCER RESEARCH, INC.

CANCER RESEARCH

This journal is sponsored by The American Association for Cancer Research, Inc.; The Anna Fuller Fund; Cancer Research Division, Donner Foundation, Incorporated; The Jane Coffin Childs Memorial Fund for Medical Research; and The Elsa U. Pardee Foundation.

Published by Cancer Research Division, Donner Foundation, Incorporated
Publication Office, 317 Maynard Street, Ann Arbor, Michigan

The annual subscription rates for one volume are: To members of the American Association for Cancer Research, Inc., $5.00; to others and to libraries, institutions, and organizations, domestic, $7.00; Canadian, $7.50; foreign, $8.00. Single copies, $1.00. Business communications, remittances, and subscriptions should be addressed to Dr. Theodore P. Eberhard, Business Manager, Jefferson Hospital, 10th and Sansom Streets, Philadelphia 7, Pa.

Entered as second class matter December 16, 1946, at the Post Office at New Haven, Conn., under the Act of March 3, 1879. Application pending transfer to Ann Arbor, Mich.

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FOREWORD

The Hodgkin's Disease Research Foundation, Inc., under whose auspices the present review was written, earnestly desires that its publication stimulate interest and research in Hodgkin's disease and allied fields of investigation. The individuals responsible for the choice of material included in these pages extend their humble apology to those physicians and scientists whose outstanding observations recorded during the years 1832-1947 have been omitted. The authors have attempted to avoid drawing conclusions from the literature which are not those of individual investigators and to avoid passing judgment on the validity of specific observations, conclusions and hypotheses. The vision and perseverance of Harry A. Rolnick, Ph.D., the Foundation's secretary and treasurer, has in large part been responsible for both the inception and completion of this project. The authors are greatly indebted to the investigators, medical statisticians and secretaries who contributed generously to the compilation of the necessary data.

A. INTRODUCTION

1. HISTORICAL REVIEW

The earliest description of Hodgkin's disease is attributed to Malpighi (353). In "De Viscerum Structura", written in 1661, "grape-like clusters" of nodular splenic lesions and lymph node enlargements found at post mortem are described. Not until 1832, however, was the syndrome evaluated as a pathologic and clinical entity. At that time, Thomas Hodgkin (239) described seven cases having in common lymph node and spleen enlargement, cachexia and fatal termination. There was no microscopic study of the involved organs and for this reason the process of definition and classification, within the broad clinical outlines set up by Hogdkin, remained for others to carry out.

Fox (163) has reported the results of the microscopic examination of three of the original seven tissues described in the gross by Thomas Hodgkin in 1832. On the basis of microscopic appearance, two of the three cases studied appeared to be Hodgkin's disease. The third case was considered to be

lymphosarcoma. On the basis of the history and clinical description contained in the paper by Hodgkin, Fox classified the other four cases as follows: one case of Hodgkin's disease, one of tuberculosis, one of syphilis, and one of "systemic lymphomatosis."

Virchow (529), in 1845, separated the general syndrome into aleukemic and leukemic subgroups. In 1865, Cohnheim (89) called the former pseudoleukemia. Wilks (551), in 1856, described 10 cases of "lardaceous disease" including three previously reported by Thomas Hodgkin (239). Wilks described the appearance of the enlarged nodes and spleen in detail and distinguished the changes observed from those of other diseases. In 1865, Wilks (552) described 15 cases (including 4 previously reported by Thomas Hodgkin) clearly separating these from the lardaceous diseases mentioned in his first paper and called the new syndrome Hodgkin's disease.

In 1872, Langhans (318) studied the histology of the lesions and noted the presence of giant cells which he described but did not sketch. Six years later, Greenfield (216) in describing the microscopic appearance of the lesions observed multinucleated giant cells, a pleomorphism of cells and an increase in fibrous tissue. Dreschfeld (138) again reported the presence of giant cells in Hodgkin's disease in 1891. One year later, Goldman (198) pointed out the frequency with which eosinophils are found. Dietrich (133) gave a detailed general description of the characteristic cytopathology in 1896. Sternberg's analysis of the microscopic appearances of the lesions and particularly of the giant cells followed two years later (492). It was not until 1902 that Dorothy Reed's classic contribution to the histopathology of the disease was made (431).

Concepts of the nature of Hodgkin's disease have undergone historical evolution. At the time of Wilks and for almost twenty years thereafter, the general conception of Hodgkin's disease was that of a "constitutional disorder resulting in a hard or soft form of lymphoma, marked clinically by large tumors of the lymph glands, enlargement of the spleen, anemia with leukocytosis, fever, and a fatal cachexia; histologically by a simple hyperplasia of some or all of the lymph glands and nodules of lymphomatous tissues in the internal organs" (431). The arguments advanced during this period for the neoplastic nature of the disease were subjected to reevaluation when Kundrat (313) and Dreschfeld (138) distinguished between Hodgkin's disease and lymphosarcoma.

During the late Nineteenth Century, the possibility that Hodgkin's disease is caused by an infectious agent received serious consideration. Waetzoldt (535) described a case of Hodgkin's disease with terminal tuberculosis in 1890. Dietrich in 1896 (133) and Fischer in 1897 (154) emphasized the differences between the two diseases. Fischer inoculated animals with diseased nodes and cultured the blood of these animals and the blood and diseased nodes of patients without finding evidence of the presence of tubercle bacilli. In 1898, Sternberg suggested the tubercle bacillus as the etiologic agent of Hodgkin's disease, a hypothesis which he later abandoned. Although Dorothy Reed believed that "tuberculosis has no relation to the subject," she concurred with the inflammatory theory of Hodgkin's disease.

Although the histopathologic description of the manifest disease is unequivocal in the majority of cases, controversy concerning its origin, nature and etiology continues. The relation of Hodgkin's disease to other disorders of the lymphoid and reticuloendothelial system remains unknown and awaits further investigation.

2. NOMENCLATURE

A comprehensive review of the literature of Hodgkin's disease through 1932, written by Wallhauser (538), lists scores of names which have been applied to the disease in the past. Failure to understand the nature and etiology of Hodgkin's disease is reflected in the confusion of nomenclature which persists in the modern literature: lymphadenoma, malignant lymphoma, malignant granuloma, adenie, lymphogranuloma and lymphogranulomatosis.

Although the *Quarterly Cumulative Index* has classified the disease under a variety of headings in the past, it is now officially indexed under the single designation of "Hodgkin's disease" not only by this group but also by the American Medical Association and the U. S. Bureau of the Census.

3. DISTRIBUTION AND INCIDENCE

Incidence and geographical distribution.—The recorded incidence of Hodgkin's disease in the United States varies from 0.5 to 2.5 per 100,000 living population (244). The coastal and north Central States record a high mortality, the number of cases reported in the northern United States being approximately twice that reported in the southern section. The study made by Hoster (244) concerning the distribution of the disease in the United States suggests that the number of cases reported from a given State varies with the reporting ability of that State, as measured by the re-

porting ability for heart disease, diabetes mellitus, and all types of cancer. It is probably true that the number of cases observed in any locality throughout the world increases as the physicians in that locality become aware of its existence (83) and are given the facilities and personnel for diagnostic biopsy. Further figures relative to the incidence of the disease may be found in Table I.

TABLE I

Investigator	Incidence
Barron (23)	0.32% Series of 7,253 consecutive autopsies.
Symmers (503)	0.16% Series of 8,485 consecutive autopsies.
Jackson and Parker (262)	0.21% Series of 16,773 consecutive autopsies.
Ciechanowski (84)	0.33% Series of 60,000 autopsies.
Uddstromer (518)	0.054 per 10,000 living persons (average from 1915-1931) in Sweden.
Isaacs (257)	1.3 per 100,000 living persons (1921).
(Metropolitan Life Insurance Statistics)	2.1 per 100,000 living persons (1934-1936).
Hoster (244)	0.04-2.4 deaths per 100,000 lives exposed (figures from 1939-1941, U. S. Bureau of Census).
Beebe (27)	2.27 new cases in the U. S. Army and Navy per 100,000 living persons during 1941-1945.
Hoster (245)	1.9 average deaths per 100,000 living persons in New York City (1931-1944).

Increased numbers of cases have been reported during the past two decades (46, 84, 518). This increase is considered by some (262, 311) to be consequent to the more widespread use of the biopsy technic as a diagnostic measure. Other investigators, however, feel that the disease is actually increasing (60, 84) and the Metropolitan Life Insurance Company figures, which compare statistics for 1921 and 1936, appear to support this opinion (See Table I); whereas data obtained from the Vital Statistics of the City of New York appear to deny it (245).

Available figures for the incidence of Hodgkin's disease in countries outside Western Europe and North America are incomplete. Nevertheless, the disease appears to have a world-wide distribution (81, 474, 538). Cases have been reported from Argentina, Brazil, South Africa, Australia, New Zealand, and Japan. In 1934, Dr. J. W. Spies of the Peiping Union Medical College commented that, "Hodgkin's disease apparently does not occur in North China." Previous to 1937, however, 13 cases were reported by the Pathology Department of the Peiping Union Medical College and the nativity of 7 was definitely known. Cheeloo University reported 14 proven cases whose nativity was given. Sung (501) described a case in a patient who came from the rice-eating section of North Anhwei and was convinced that he had seen other cases although they were not subjected to diagnostic biopsy. Bercovitz (34) reports 2 cases both confirmed by biopsy from Hainan, a Chinese island. Bercovitz reports that "tuberculosis and lymphoma are common in Hainan," but that "Hodgkin's disease seems very rare."

Age.—Hodgkin's disease may occur at any age (201). Charache (79), Chiari (81), Priesel and Winkelbauer (423) and Davis (122) each report a case of a child born with the disease. Charache (79) found 4 reported cases in infants between the ages of 2 and 5 months. Although the disease occurs throughout childhood, it is said to begin only rarely during puberty (262, 538). It is seen most frequently in young adults, especially during the third decade. Hoster (246) reported the age distribution of 759 cases tabulated by the New York City Department of Health from 1940 to 1944. He states, "The curve for males reaches a peak in the 45 to 49 year age group and the curve for females in the 25 to 29 year age group." Cases are reported to occur as late as the ninth and even the tenth decade. The "sarcomatous" form of the disease is thought to occur more frequently in the middle-aged and elderly (262).

Recently, the suggestion has been advanced that apparent rather than true age distribution variations exist in the disease. Bersack (35), for example, believes that the number of patients in each decade who develop Hodgkin's disease is proportional to the number in the general population in the corresponding decade.

A summary of the incidence of Hodgkin's disease in the age groups of selected series of cases recorded in the United States and Europe together with the age distribution of the general population in those areas covered by the series is presented below.

Sex.—Hodgkin's disease is said to occur more often in the young adult male. Wallhauser (538) collected a total of 1,447 cases, 1,009 of which were males and 438 females. Since 1933, the year of Wallhauser's report, 2,601 cases have been gath-

TABLE II

	No. in Series	Age 0-9	10-19	20-29	30-39	40-49	50-59	60-69	70 & over
Percentage of each age group of Hodgkin's patients in U. S. outside of New York City	680	8.8	15.9	22.6	19.0	15.3	10.6	6.3	1.5
Percentage of each group in general population in U. S. in 1920 (23, 59, 127, 262, 336)		21.7	19.0	17.4	15.0	11.5	7.9	4.8	2.7
Percentage of each age group of Hodgkin's patients (at time of death) in New York City (1941-1944)	759	0.4	6.6	17.8	18.5	19.1	17.4	13.2	7.0
Percentage of each group in general population in New York City in 1940 (244)		12.6	15.8	18.2	18.2	15.9	10.1	6.2	3.0
Percentage of each age group of Hodgkin's patients in Sweden (1915-1936)	536	6.3	9.1	23.8	19.0	13.8	14.2	11.0	2.8
Percentage of each age group in general population in Sweden (518)		18.1	18.8	16.8	13.9	11.6	8.6	7.6	4.6
Percentage of each age group of Hodgkin's patients in Europe (outside Sweden) (20, 92, 354, 458, 493, 506, 570)	735	8.3	14.0	27.6	20.8	13.9	9.9	4.8	0.7

ered from the literature, 1,612 males and 989 females. Metropolitan Life Insurance data indicate that in 1936 60% of deaths due to Hodgkin's disease were among males.

TABLE III

	Males Number	%	Females Number	%
Cases up to 1933 (538)	1,009	69.7	438	30.3
Cases since 1933 (18, 58, 92, 192, 200, 245, 262, 309, 321, 477, 518)	1,612	62.0	989	38.0

In Jackson and Parker's series of 41 paragranuloma cases 73% were male, of 287 granuloma 70% were male and of 51 sarcoma cases 51% were male.

Sex differences are more pronounced when the disease occurs in childhood. An analysis of figures taken from studies of children with Hodgkin's disease indicates that 83% were boys (79, 200, 280, 479, 538).

Conflicting statements concerning the relation of age and sex appear in the literature. These are too often based upon opinion alone. The statistical evidence available at present permits one to conclude little more than that males are affected almost twice as often as females, and that in children the ratio increases to more than 4:1.

It is perhaps pertinent to reemphasize the fact that all forms of lymphoma are more common in the male than in the female (259). In lymphatic leukemia in adults, the ratio is 3:1 in favor of males; however, in the early years of life, females are affected more frequently than males (387). Sixty per cent of myelogenous leukemia is said to occur in males and forty per cent in females (386).

Race.—It is probable that individuals of all races are capable of developing Hodgkin's disease but exact information concerning variations in the susceptibility of different races is not available. Some authors (81, 237) maintain that there is no ethnic factor in the etiology of this disease but others assert that the disease is distinctly less common among Negroes than among the white population (122, 336, 474). This observation is thought to be particularly true in instances occurring during childhood (79).

A few reported statements concerning distribution among races are recorded in Table IV.

It would appear that racial factors are of no clear-cut significance in the development of Hodgkin's disease in adults although specific analysis of this phase of the subject has been meager.

Familial incidence.—Hodgkin's disease has been reported sporadically in 2 or more members of the same family (478). It is asserted that this occurs more often than can be accounted for by chance alone (128). Twenty reports of familial disease have been assembled, and are briefly summarized:

1. The patient, a young female, developed Hodgkin's disease. Five years previously, her father died of what was thought to be Hodgkin's disease. Four years after the daughter's illness was diagnosed, the mother developed the disease (208).

2. A boy died of Hodgkin's disease at the age of 18 years; many years later his brother was similarly affected (54).

3. Two brothers, one 11 and one 13 years of age, developed Hodgkin's disease within one week of each other. The boys died two years later within a space of 2 months (369).

4. A man of 30 years, a cheese-maker, developed Hodgkin's disease in 1924 and died in 1927. In 1924, his sister married a cheese-maker and moved to another part of France. She developed Hodgkin's disease in 1934 at the age of 34 (192).

5. A man died of Hodgkin's disease and shortly thereafter his child developed the same disease (280).

6. A girl, whose sister and cousin had died of Hodgkin's disease, developed the disease at the age of 21 years (479).

7. A boy of 9 died of Hodgkin's disease and his brother developed the disease a short time later (479).

8. Three siblings developed Hodgkin's disease; the diagnosis of each was confirmed by biopsy (96).

9. A man died at the age of 34 years from what was diagnosed as "mediastinal tumor." Twenty one years later his son died of mediastinal Hodgkin's disease and 4 years after that a male cousin died of the same disease with the same localization (11).

10. All children of a father who had Hodgkin's disease "were subject to enlargement of the lymph nodes" (396, quoting Muller 1867).

11. Warner (542) reports two sisters with Hodgkin's disease.

12. Hodgkin's disease developed in 4 year old twins, both of whom had had measles and adenitis before the onset of the disease (412).

13. Three children were born with Hodgkin's disease; their mothers had the disease (79, 82, 122, 423).

14. Branch (45) presents a case of "congenital lymphoblastoma" in an infant 2 months old.

15. A man of 33 years died of Hodgkin's disease in 1915. His son developed the disease at the age of 28 in 1940 (243).

16. A woman, aged 33, had Hodgkin's disease. Her father died of Hodgkin's disease and her mother had polycythemia vera (184).

17. An uncle, "old," and a nephew, "middle aged," blood relatives, developed Hodgkin's disease (59).

18. Two brothers in their teens developed Hodgkin's disease (59).

19. Koranyi (304) mentions 2 brothers who died of Hodgkin's disease.

20. Uddstromer (518) reports the finding of 3 patients with Hodgkin's disease in one family (2 sisters and 1 cousin). Two years following the death of one sister the cousin became ill, and 4 years later the other sister became ill with Hodgkin's disease.

In contrast with these reports are large series of cases occurring in only one member of each family. One member of pairs of homologous twins have been reported to have Hodgkin's disease in 5 instances, the other member remaining unaffected (77, 78, 479). Numerous pregnancies in women with Hodgkin's disease have not resulted in diseased offspring except in the rare instances cited.

TABLE IV

Name	Number of Cases	Figures		
Burger and Lehman (58)	54	16.7% Negroes; 15.6% of all admissions are Negroes		
Oakey (403)	52	No Negroes; 10% Negroes in population		
Levitt (325)	29	No Negroes		
Charache (79)	185 children	4 Negroes, 181 whites		
Kaplan (280)	16 children	All white "even though a large Negro population attends the hospital"		
Goldman (200)	212		General Admissions by race and nationality	Percentage of all Hodgkin's disease by race and nationality
		Jews	21%	20%
		Italians	5.6%	19%
		Negroes	4%	6%
Hoster (245)	759	3.0% of deaths due to Hodgkin's disease were Negroes (Negro population in New York City 6.4% of total).		

It is difficult to evaluate the significance of the conflicting reports available. Although the assembled evidence suggests a familial incidence, there is no information to indicate whether this evidence, if established, is on the basis of genetic or environmental influences.

B. PATHOLOGY

1. GROSS PATHOLOGY

Although Hodgkin's disease is considered to be a disorder of the entire reticuloendothelial system, it affects the lymphatic elements predominantly. The nodes of the neck appear to be involved first in a majority of cases. Early, unilateral lymph node disease is said to be the most frequent type of involvement; lymph nodes are more often involved on the same side in two regions than on both sides in one region (41, 332, 367). Disease of the neighboring nodes, "apparently following the normal lymph distribution," may occur progressively (171, 431). The rate of spread is variable and progression occurs by successive exacerbations and remissions. If the patient lives long enough, generalized spread to the deeper nodes and to the viscera and bones is inevitable (18). In order of frequency, the nodes reported to be involved are as follows: cervical, axillary, mediastinal, retroperitoneal, inguinal and epitrochlear.

Some investigators maintain that involvement of

the deeper lymph nodes is primary in the vast majority of cases and that superficial lymphadenopathy observed first by the physician merely appears to be primary (504). Slaughter and Craver (477), for example, state that lymphadenopathy observed first in the left neck is due to "commencement of the disease internally with passage through the thoracic duct, thus appearing first in the left neck." Symmers (504) has written the following: "It is a matter of clinical value that enlargement of axillary nodes suggests predominant involvement of the thoracic nodes and that inguinal adenopathy suggests predominant involvement of abdominal nodes. If enlargement of superficial nodes occurs, it is a late signal and indicates that the disease has attained widespread proportions in the abdomen or in the abdomen and thorax. . . . The lymphoid diseases occur most frequently in the deeper lymphoid structures, while the enlargement of superficial nodes is of secondary significance." Baker and Mann (18), on the other hand, contend that deep disease very rarely occurs without superficial lymph node involvement. They further maintain that in their series of sixty-five cases, when more than one lymph node area was involved, the cervical group was always one of the areas affected.

The lymph nodes are frequently enlarged in chains. There are often 3 to 5 enlarged nodes in each affected group, varying from 2 to 12 cm. in size. The degree of hardness varies with the duration of their enlargement. The smaller nodes are often soft and elastic, the larger ones hard; and nodes of differing consistency are usually present in the same group. The nodes may be freely movable and discrete, or matted, as in the invasive or late stages of the disease (200, 287, 431, 474). The nodes first affected may attain large size, while those involved later are usually relatively smaller (455).

"On section, the entire node is found to be completely changed by the process; the older growths show a semi-translucent gray surface, broken by opaque, intersecting yellowish lines of fibrous tissue" (431). There may be occasional foci of yellowish gray necrosis and rare small areas of hemorrhage. The younger growths show a uniform gray surface, more opaque than normal and bulging on section (431). Suppuration is rare and is probably due to secondary infection (192, 431, 493). However, Harrell (227) cites a case of fulminating Hodgkin's disease which was characterized by much pus formation and necrosis with very little fibrosis. No secondary invader was identified. Similar cases are sporadically reported.

"The involvement of internal organs is just a question of time; though Hodgkin's disease is primarily selectively lymphatic, it results in a compensatory lymphogenesis in other organs with subsequent involvement" (114).

(a) LOCALIZATION OF LESIONS

Spleen.—Splenomegaly may be an important part of the clinical picture of Hodgkin's disease and the disease may be primary in that organ (504). The spleen has been found enlarged in 56 to 78% of a combined group including both clinical and postmortem observations (18, 266, 455, 474, 504, 518, 571). In early cases it is rarely palpable but as the disease runs its course, the organ usually becomes enlarged. One author states that, in almost 100% of the cases observed at post mortem, the spleen is hypertrophied (201). The postmortem spleen is described as firm, red and dense, and showing foci of necrosis (287). The lesions are usually miliary or sub-miliary but they occasionally attain large size (538), are grey-white, sharply demarcated and have round or irregular outlines.

A definitive study made by Goldman (200) revealed the following:

89 early cases	Splenomegaly in 3
123 late cases	Splenomegaly in 64
34 autopsies	Splenomegaly in almost 100 per cent

Liver.—Though less susceptible than the spleen, the liver is said to be involved by the Hodgkin's process in 50 to 60% of cases (474, 504, 518, 538). Goldman's study of 212 patients revealed hepatomegaly in 1 of 89 early cases and 45 of 123 late cases of Hodgkin's disease. Although the liver may not contain gross lesions, it is usually enlarged and careful examination reveals microscopic foci (287). As in the spleen, however, the hepatic lesions may attain considerable size and are often grey-white and sharply demarcated with round or irregular outlines.

Primary hepatic disease is unusual but has occurred (504) and lesions of the liver have been reported in patients whose spleens were free of the disease (474, 504). Ordinarily, hepatic lesions are part of the generalized involvement of abdominal and thoracic structures.

Jaundice is found in 3 to 8% of patients (18, 200, 518) and may be due to pressure of enlarged nodes on extrahepatic biliary ducts. Harrell (227) reported a case with Hodgkin's disease of the gall bladder.

Of considerable interest are the rare occurrences of otherwise uncomplicated Hodgkin's disease which show amyloid deposits in the liver (81).

Gastrointestinal tract.—Intrinsic lesions of the gastrointestinal tract are said to occur in only 1 to

4% of patients (106, 200, 265) but the cases are often so dramatic that they are reported with relative frequency. The majority of these patients are in the fifth decade and men are affected twice as often as women (106, 465). Gastrointestinal Hodgkin's disease involves principally the stomach and upper part of the small intestine (95, 493). The lesions may be part of the disseminated disease or may be limited to the gastrointestinal tract. The latter is the more rare, although primary isolated Hodgkin's disease of the stomach has been reported by Avent (13) and Singer (475); a case of Hodgkin's disease limited to one area in the ileum has been described by Spangler (481); 7 cases of primary duodenal Hodgkin's disease were collected by Pusch (426); and Symmers (504) reported that, in a series of 173 necropsies in Hodgkin's patients, not one example of involvement of the gastrointestinal tract was found. In a discussion of one of the cases of this type at the Massachusetts General Hospital (66), it was asserted that "in any series of cancer of the small bowel, one-half would be due to lymphoma."

Usually the lesions in the gastrointestinal tract result from direct extension from neighboring lymph nodes or from involvement of lymph follicles. The lesions appearing on mucosal surfaces may be ulcerative while those in the wall may be tumor-like. The latter may be localized or diffuse, are usually moderately small, pearly white, flat or nodular, but may attain large size and are often palpable during life (482). Involvement of the gastrointestinal tract may be extensive without concomitant mesenteric, hepatic or splenic disease (65, 538).

Other intra-abdominal organs.—Involvement of all the organs of the body is possible and has been reported in most instances (518). The pancreas (219), adrenals (336), kidneys (336), and, in fact any organ containing collections of lymphoid tissue is not immune. Extensive disease of the pancreas or adrenals may occur without the development of diabetes or Addison's disease (536). Adrenal glands were involved in 11% of Jackson and Parker's cases and 2% of Uddstromer's 192 autopsied cases (518). Renal impairment may be due to pressure on the ureters with the development of hydronephrosis (200) or may follow involvement of the cortex (474). The uterus and ovaries have been described as a site of Hodgkin's disease (538). Phillips (418) describes a case of Hodgkin's disease of the urinary bladder which was successfully diagnosed and treated during life. Cystoscopy revealed grey-white nodules the size of grape seeds on the bladder mucosa. Urethral Hodgkin's disease was seen in a patient with inguinal adenopathy (96). A case of Hodgkin's sarcoma involving the left kidney, ureter and bladder is described by Lebowitch (493).

Lesions of the peritoneum are less common than those of the pleura but have been reported in about 5% of cases (266). When extensive abdominal Hodgkin's disease is present, death due to peritonitis is not uncommon (538).

Hodgkin's disease is found confined to the abdominal cavity in as many as 8% of cases (201).

Intrathoracic organs.—Intrathoracic localization may occur in the mediastinal lymph nodes, lungs, heart or chest wall (518). Lesions in the chest cavity are not infrequently found early in the disease and 40 to 60% of patients develop intrathoracic lesions at one time or another during the course of the disease (18, 526, 560). In a series of 214 cases, Peirce, Jacox and Hildreth (414) reported that roentgenographic evidence of intrathoracic disease was far greater than suggested by clinical signs and symptoms.

Disease of the mediastinal nodes is the most common form of intrathoracic involvement and is said to be observed in about 50% of cases (265, 518). Localization in this area is usually manifest within three years after the onset of the disease (265). Lesions may become smaller or larger unaccountably and the size and density of x-ray shadows may increase and decrease during the life of the patient (433). Children present evidence of mediastinal disease with great frequency (280) and massive enlargement of the mediastinal nodes is characteristic of the early rather than the later decades (265).

The lungs are involved in 15 to 35% of cases (103, 150), possibly in proportion to the diligence with which this type of lesion is sought. Craver finds 34% in his series of 297 cases (103), Uddstromer 33% of 192 cases (518), while Goldman reports less than 8% among his 319 patients (201). The lungs may be the primary site of the disease (80, 474, 526). In the great majority of reported cases, however, the pulmonary lesions are said to be secondary to spread from other foci, directly from mediastinal nodes or from more distant sites by way of the lymphatics or blood stream. It has been postulated that the lesions vary according to their mode of spread; if they result from direct extension, they originate near the hilus and extend fanwise through the lobe of the lung. If brought by the lymph stream, the lesions spread along peribronchial and interlobar lymphatics; and if the route is hematogenous, discreet nodules may be found scattered throughout the lungs (200, 474, 526, 538, 560). Pulmonary Hodgkin's disease has

been associated with the development of numerous unusual pathologic complications including cavitation, tracheobronchial fistula, panbronchitis, peribronchitis, bronchial stenosis and pedunculated endobronchial masses (174, 201). Atelectasis and emphysema may be found as a consequence of the abnormal pressure relationships exerted by the presence of diseased tissue. The complications enumerated are said to be due to Hodgkin's disease alone and not to additional intercurrent diseases.

TABLE V: PERCENTAGE INCIDENCE OF PULMONARY LESIONS IN LYMPHOMAS (CRAVER ET AL. [103]).

Authors	Hodgkin's Disease	Lymphatic Leukemia	Lymphosarcoma
Kirklin and Hefke (Roentgen examination)	15	8	4.6
Versé (autopsy)	33	—	—
Falconer and Leonard (Roentgen and autopsy examination)	31	30	36
Moolten (autopsy)	50	—	—
Memorial Hospital (Roentgen examination)	34	11	12
(autopsy)	64	—	39

Pleural effusions are a frequent complication of intrathoracic Hodgkin's disease and occur in 35% of Jackson and Parker's cases (266) and 20% of Uddstromer's (518). Involvement of pleural surfaces may occur but is rare, and most effusions are thought to result from pressure on hilar lymphatics and blood vessels by enlarged mediastinal nodes. It is unusual to find bloody fluid, and examination for characteristic tumor cells is reported as negative (201). Rare complications include chylous pleuritis and empyema.

Garvin (183) made a diagnosis of Hodgkin's disease of the myocardium and treated it with temporary benefit. At autopsy both atria were found to be involved in this very unusual case. Pericardial complications are reported less rarely than myocardial; 2% of autopsied cases are said to present evidence of pericardial lesions (266).

Bone.—Full awareness of the frequency with which bone is the site of Hodgkin's disease has developed only during the past few years. Gross lesions of the bone are rarely apparent during life and are therefore frequently overlooked. Bone lesions are said to be a rather late manifestation (139, 273, 490, 528), are associated with chronicity of the disease and rarely develop in acute cases (265). Dresser and Spencer (139) report 30 cases with an average length of life of 3.5 years from the onset of symptoms and an average length of life of eleven months following roentgen demonstration of bone involvement. Primary osseous Hodgkin's disease has been reported (303) but the evidence that it is primary is equivocal (265, 528). Secondary lesions are found in 6 to 23% of cases, the variation in findings apparently being dependent on the care with which the search is made (104, 201, 265, 490).

The sites of predilection for the bones parallel closely those in which red marrow is present. In the order of frequency of involvement they are: vertebrae, pelvis, ribs, femur, sternum and skull (104, 201, 303, 490, 518, 528). Osteolytic, osteoblastic or mixed reactions are possible; the last is found in almost 50% of cases (528).

Almost 100% of patients are said to show disease foci in the bone marrow if a careful search is made (490, 528). Most of these changes are microscopic but macroscopic lesions are also described. Sternal aspiration will rarely reveal Sternberg-Reed cells; and serial section taken from several locations are often necessary before foci are demonstrable in the marrow.

Central nervous system.—Specific changes in the tissue of the central nervous system are rarely reported. Presumably neurologic symptoms are due to epidural, subdural or vertebral lesions, invasion of the lymphatics of the cord, myelomalacia secondary to obstruction of vessels and lymphatics and meningitis or toxic myelitis (7, 213, 266). Because vertebrae are often the site of lesions—Uddstromer (578) reported 12 in a series of 192 autopsied cases—transverse myelitis is a complication in as many as 5% of Goldman's series (200). When the cord is involved, the level of involvement is thoracic in about 80%, cervical in 15% and lumbosacral in about 5% of cases (548). Ginsburg (195) has reported invasion of the central nervous system in 10 of 36 cases.

Very rarely, direct invasion of the tissue of the central nervous system occurs. This is most frequently seen in the "sarcomatous" type of Hodgkin's disease. Jackson and Parker (266) describe 1 thalamocortical and 3 cerebellar lesions. An exceptional case of invasion of the brain, reported by Winkleman and Moore (555) was thought to be on a hematogenous basis since no lesions were seen in the dura.

The production of encephalitis in rabbits by means of the Gordon test has excited interest in the central nervous system aspect of the disease. However, only two cases of Hodgkin's disease have been reported in which the non-infectious encephalitic phenomenon was observed. In one of these, diffuse leptomeningeal and perineuronal infiltrations were responsible for the symptoms (302). Bateman, Squires and Thannhauser (25) describe Schilder's disease associated with Hodgkin's disease in a pa-

tient whose brain at death showed widespread damage and edema and whose specific Hodgkin's lesions were confined to the abdominal and thoracic regions. These authors suggest that the profound destruction of the central nervous system could have been the result of the activity of a toxic agent associated with the Hodgkin's disease process. In support of this possibility are sporadic reports of posterolateral or other tract degenerations occurring in the course of the disease without discernible pathologic cause (93, 463).

Skin.—Varied and perplexing skin lesions are found during the course of Hodgkin's disease. Twenty to 40% of patients have significant complaints referable to the skin (18, 60, 69, 200, 464, 474, 518, 538); however, many of these are limited to itching and excoriation produced by scratching. Skin lesions whose cytopathology was similar to that observed in Hodgkin's nodes were first described by Grosz (218) in 1906. Ulcerated or nodular lesions whose cytopathologic appearance is typical of the Hodgkin's process are not common but are seen in almost every group of cases. The "id" reactions are found 5 to 10 times more frequently than the Hodgkin's type lesions and include maculopapules, hemorrhagic lesions, urticariae, bullae, vesicles, pigmentation, dryness, hyperkeratosis, exfoliative dermatitis and alopecia (60, 324, 464).

Hodgkin's disease of the skin may be primary (433, 538). The specific lesions often ulcerate; they may be widely disseminated or localized (60, 246). Localization has been observed in some cases over involved lymph node areas (60). One case of miliary spread to the skin is described (36). The subcutaneous tissues and mucous membranes appear to be relatively immune (201, 502). Diagnosis of a section of diseased skin may be very difficult since the morphology of the lesions in this location is often similar to that of other cutaneous lymphomas (140).

Other sites.—As mentioned above, almost every organ in the body has been reported to contain typical lesions (518). Eleven cases of Hodgkin's disease of the breast are described, 8 occurring on the right and 3 on the left side (3). Two per cent of patients with Hodgkin's granuloma and 11% of those with "sarcoma" were observed to have nasopharyngeal or tonsilar lesions and some of these were reported as primary foci of the disease (266). The tonsil and the thymus are considered by Steiner (486) to be relatively immune to the Hodgkin's process. Ringold (84) reported 4 cases of Hodgkin's disease primary in the tonsil and Symmers (504) 8 cases (including 5 of his own) primary in the thymus. Sternberg (493) noted 5 cases of tonsil involvement in a series of fifty two cases. Laryngeal lesions are seen infrequently (538). Cases of Hodgkin's disease of the thyroid are reported by Sternberg (493), Jackson and Parker (269). Avery (14, 15) and Warren (541) describe an interesting Hodgkin's lesion of the eye which responded well to roentgen therapy.

Skeletal muscle has been reported as a site of disease involvement (474).

(b) PRIMARY SITE

The distribution of lymphoid tissue throughout the body is widespread; some important lymphoid tissue aggregates are so situated that neither physical examination nor x-ray can give important information concerning their size and consistency. It is therefore impossible to say with certainty that Hodgkin's disease starts in a given place in a given patient. Since early lesions of the disease are frequently symptomless, it is inevitable that enlargement should be discovered more frequently and earlier in the superficial than in the deep seated node groups. There is, however, indirect evidence derived from autopsy material that superficial lymph node disease is truly primary in many cases. Study of large series of cases suggests that deep-seated disease rarely occurs without superficial involvement (18, 201, 266). Superficial adenopathy may be present for months without the development of constitutional symptoms, and eradication of the superficial lesions by surgery or heavy doses of x-ray has produced remissions which have lasted for years in many patients (477, 511, 567). Slaughter and Craver (477) and Symmers (504), nevertheless, believe that the disease commonly begins in the internal nodes, possibly having gained access to them through the gastrointestinal tract, lungs or upper respiratory tract. Superficial involvement is considered to be rather late chronologically in relation to the onset of the disease. Desjardins (124) maintains that the para-aortic nodes are primary "more often than is commonly supposed."

The most frequently apparent site of onset is the left cervical region (41, 60, 113, 237, 477, 479). The apparent sites of onset in other lymph node groups in order of frequency are as follows: both sides of the neck, axillary nodes, mediastinal nodes, retroperitoneal nodes, inguinal nodes, epitrochlear nodes (this information was compiled from 18, 41, 60, 114, 403).

Organs other than lymph nodes have been considered the primary site of Hodgkin's disease in some cases: spleen (504), liver (504), stomach (13, 84, 493), duodenum (426), ileum (481), lungs (474), thymus (504), bone (490, 538),

breast (493), bone marrow (490) and skin (433). Primary localization in these sites, however, is considered rare. The fact that conclusions of this kind are frequently reached at operation rather than at autopsy may add to their importance.

Morphologic evidence of origin in a specified area derived from surgical or postmortem exploration is not always conclusive. Enlarged lymph node groups palpated during life may disappear spontaneously during the course of the disease and careful search at autopsy may fail to reveal their presence.

2. Histopathology

The earliest detectable change in lymphoid tissue, the site of Hodgkin's disease, is said to be a proliferation of reticulum cells with increased number of mitoses in these cells (431, 470). The proliferation is accompanied by dilatation of blood vessels and lymph sinuses. As the process advances, the lymph and reticular spaces become filled with proliferating reticulum cells and lymphocytes with obliteration of the distinction between follicles and sinuses. During this proliferative period, large epithelioid cells with vesicular nuclei appear as may also giant cells with one or more nuclei and prominent nucleoli. Occasionally, very large giant cells with many small nuclei peripherally arranged are seen. Plasma cells are found in large numbers and eosinophils are often abundant except in the germinal centers. It is not uncommon, however, to observe a node in which few or no eosinophils are found. There may be a marked multiplication of connective tissue cells resulting in their numerical predominance. Areas of ischemic necrosis and hyalinized fibrous tissue may be noted.

Fraser and Mekie (171) outline the histopathologic evolution of Hodgkin's disease as follows: (a) proliferation of reticuloendothelial lymphocytic tissue; (b) disturbance and disruption of the natural evolution and development of the "lympho-reticuloendothelial group" of cells so that many cells of immature types appear; (c) development of the following cellular elements: eosinophils, multinucleated cells and large mononuclear cells; (d) conversion or "degeneration of cell elements into fibrous tissue."

The established lesions form a polycellular mass made up of lymphocytes, endothelial cells, megakaryocytes, Langhan's giant cells, myelocytes, Sternberg-Reed cells and lymphoblasts. Any of the cell types mentioned may predominate while others may be subordinate in numbers or entirely absent (538). The lesions are diffusely distributed throughout the extent of the nodes (474). Necrosis is rarely prominent and is usually of the coagulation type; the cause is variously assigned to ischemia, local anaphylaxis, or secondary infection. Involvement of the capsule is described (474). It is said that lymphocytic infiltration precedes the granulomatous change when it occurs.

The individual cell type is described and discussed by Reed (413): Reticulum cells are said to be of the same origin as the free cells of the germinal centers and both are thought to produce lymphocytes. The connective tissue arises from three sources: the trabeculae of the node, the connective tissue supporting and surrounding blood vessels and the transformation of reticulum cells to fibroblasts. Large giant cells are derived from reticulum cells through a series of changes in which the epithelioid and large mononuclear cells are considered stages in the transformation to the giant cell. The latter is free, has irregular cytoplasmic processes, homogeneous protoplasm, large nuclei which are round, bean-shaped or irregularly indented, with a prominent chromatin network and an oval nucleolus. The giant cells contain no mitotic figures; and bizarre and irregular nuclei may be found in these cells in advanced stages of the lesions. In referring to the Sternberg-Reed cell, Hoster (245) describes the occasional occurrence of "a pale area adjacent to, and often indenting, the nucleus or nuclei. The border of this area is neither abrupt nor sharply circumscribed. There is, on the contrary, a gradual transition from the pale area to the more dense granular cytoplasm of the rest of the cell. When there are many nuclei present the pale area often occupies the center of the cell, and as previously noted, an apparent indentation of the nucleus may occur." No attempt is made to explain the significance of this observation.

Finding Sternberg-Reed cells in the lesions of monilial origin in a case of Hodgkin's disease complicated by that infection, has led Haythorn (228) to suggest that Sternberg-Reed cells may be of the wandering type and that they may respond to inflammatory stimuli outside of Hodgkin's nodules as do other wandering cells and blood elements. In tissue culture Mankin (311) found that "the essential Hodgkin's cells grew like reticulum cells and even displayed phagocytosis."

The lymphocytes are usually of the small variety and uniform in size; they are abundant early but few in number later on. The plasma cells are of unknown derivation although Pappenheim (Reed [431]) maintained that they were "undifferentiated forms of the spindle cells of the fixed tissue, and may form spindle cells under certain circumstances." The eosinophils may be distributed

throughout the lesions except in the capsule, connective tissue and germinal centers; they are rarely seen inside blood vessels. Their morphologic appearance is similar to the eosinophils of the blood and Reed attributes their presence to a chemotactic substance in the proliferating tissues. Kugelzellen, endothelial phagocytic cells, mast cells, Russel or fuchsin bodies and Charcot-Leyden crystals are found, but their presence is neither diagnostic nor characteristic. The last structure has been linked to the eosinophil (365, 511).

Hodgkin's disease presents the same essential histologic characteristics wherever it is found. Certain special characteristics of skin lesions should be noted. In a case of Hodgkin's disease cited by Bersack (36) with terminal miliary spread to the skin, biopsy of the early skin lesions showed a normal epidermis with "minimal reaction" about several small blood vessels. The change observed consisted of slight endothelial and fibroblastic proliferation. A moderate number of lymphocytes were distributed throughout the corium. Biopsy of the lesions at a later date revealed Hodgkin's disease. Rae (428) described a case of Hodgkin's disease with pruritis in which the connective tissue of the skin was infiltrated by lymphocytes.

When the typical lesions in the skin have become established, further changes consist of greater diffusion and tumefaction and more necrosis (433).

A further observation of significance is the depletion of lymphoid elements in the spleen and to a lesser extent in other organs irrespective of specific involvement by manifest lesions of Hodgkin's disease. The reduction in lymphoid elements is less pronounced but nevertheless striking in non-involved organs as compared with involved organs (442).

In 1943, Bersack (35) reviewed the microscopic anatomy of 225 cases of Hodgkin's disease and analyzed the architecture, individual cellular components and stroma of the lymph nodes. He concluded that "in the great majority of cases, there is sufficient uniformity in the several sections of one lymph node or in several simultaneous biopsies from varying sites to warrant the characterization of each case on the basis of histology." He suggests the following pathologic nomenclature:

1. *Hodgkin's lymphoreticuloma.*—Prevalence of reticulum cells or frequent mitoses, or both: (a) typical, (b) atypical.

2. *Hodgkin's lymphoma.*—Destruction of gland architecture, slight tendency to pleomorphism, Sternberg-Reed cells may be absent, moderate persistence or prevalence of lymphocytes, usually of the small variety.

3. *Hodgkin's granuloma.*—Majority of cases, typical pleomorphism, Sternberg-Reed cells, moderate fibrosis.

In 1937, Jackson (258) and in more detailed form in 1944, Jackson and Parker (262) proposed a classification of Hodgkin's disease consisting of three histologic types: paragranuloma, granuloma and sarcoma, with the following characteristics:

1. *Paragranuloma*

a. Nodes usually in the neck, few in number, rubbery, not attached to surrounding tissues, less than 3 cm. in diameter, no softening or necrosis and capsule intact; involvement of internal organs rare.

b. Architecture variably altered.

c. Sternberg-Reed cells common but containing few mitoses.

d. Adult lymphocyte the predominant cell.

e. Plasma cells and eosinophils sometimes present.

2. *Granuloma*

a. Usually involves isolated lymph node groups but may be widespread; retroperitoneal or paraaortic lymph nodes are the most frequent primary sites although on palpation the neck seems to be the first site of involvement; nodes are hard with gray white centers, homogeneous or with foci of necrosis.

b. Complete loss of architecture.

c. Pleomorphism and Sternberg-Reed cells.

d. Capsule may be involved.

e. Increase in reticulum fibers and lymph node sclerosis; necrosis and fibrosis characteristic.

f. Mitoses not uncommon.

g. Sternberg-Reed cells rarely phagocytic and tend to undergo necrobiosis.

h. Lymphocytes and plasma cells usually numerous; eosinophils and polymorphonuclear leukocytes may be numerous.

i. Occasionally, large amounts of lipid are found in the reticulum cells and in giant cells of foreign body type.

j. Involvement of any organ except the central nervous system is possible; bone marrow involved in the majority of cases.

3. *Sarcoma*

a. Usual origin is in retroperitoneal nodes with direct extension to the abdominal viscera; large conglomerate mass of varying consistency; areas of necrosis often visible.

b. Sternberg-Reed cells and other unclassified cells two to three times the size of a normal lymphocyte; the authors believe these latter cells to be the undifferentiated form of the Sternberg-Reed cell.

c. Lymphocytes and reticulum cells seen, but rarely plasma cells and eosinophils.

d. Large percentage of metastases to the gastrointestinal tract. Spleen much less often involved than in granuloma; central nervous system tissue involved in 15% of cases.

Jackson and Parker's classification is summarized as follows: "Hodgkin's paragranuloma . . . appears to be a disease essentially of lymph nodes. With the passage of time, it may become transformed into the more malignant Hodgkin's granuloma. Hodgkin's granuloma . . . may involve any organ in the body with the exception of the central nervous system and is frequently widespread. Hodgkin's sarcoma . . . behaves like a true tumor, is highly invasive and malignant and may involve any organ in the body including the central nervous system. Transitional forms of these three types of Hodgkin's disease occur, but it is essential to the understanding of the clinical features to recognize each."

Custer and Bernhard (117) using the classification of Jackson and Parker, have analyzed a series of 200 cases studied at autopsy and 500 cases at biopsy with the following results:

TABLE VI

	Autopsy	Biopsy
Hodgkin's paragranuloma	7	93
Hodgkin's granuloma	120	378
Hodgkin's sarcoma	73	29

The term Hodgkin's sarcoma has been variously applied during the past decade. Ewing (147) observed that there were unquestionably cases of Hodgkin's disease in which there was sarcomatous transformation and applied the term Hodgkin's sarcoma to highly "invasive," rapidly progressive types. Warthin (543) described Hodgkin's sarcoma as an actively growing, diffusely cellular rather than nodular lesion, with few or no eosinophils or Sternberg-Reed cells and with a tendency to infiltrate and metastasize.

Exception is taken to the classifications of Bersack and of Jackson and Parker by Slaughter and Craver (477) who maintain that no classification on a histopathologic basis is possible since lymph nodes are in all states of cytopathologic variation in the same individual at one time. Long before this controversy about classification began, Reed (431) and Longcope (336) carefully noted that in any group of diseased nodes removed from a single region, the so-called early as well as the later stages of cytopathologic alteration are to be found. Rosenthal (442) attempts to overcome this objection by maintaining that "several biopsies are required to determine the actual status of the disease since not all nodes in a given instance pass through the same stage at the same time. A single node, however, may indicate the trend of the process."

The origin and nature of the cells comprising the histologic picture of Hodgkin's disease is still a matter of controversy and will be discussed in another section of this review.

C. Clinical Aspects

1. MEDICAL HISTORY

It is often true that the patient who is found to have Hodgkin's disease gives a history of having been in excellent health previous to the onset of symptoms. In some cases early adenopathy may be present without systemic symptoms (18, 81, 200, 201, 474, 538.) Nevertheless, factors in the recent past medical history have been considered significant in predisposing an individual to the disease (245). However, in identical twins, with environment and medical history presumably similar, one member has developed the disease while the other remained unaffected (78, 479).

Many authors relate the onset of Hodgkin's disease to infection about the head and neck or to chronic or recent upper respiratory disease (238, 322, 367, 397, 455). Simmons and Benet (470) report 4 cases that appear to have started after upper respiratory infections: 3 after grippe and 1 after acute tonsillitis. Limper (330) says that acute upper respiratory infection, abscessed teeth or one of the acute exanthemas of childhood may precede the onset of the disease. Arkin (11) reports a case preceded by sore throat, tonsillar abscess, measles and bronchopneumonia. Another case had measles, frequent attacks of tonsillitis and two episodes of diphtheria before Hodgkin's disease began. Five cases by Burnham (59) occurred following tonsillectomies. In two of Kruger and Meyer's cases (309) the onset of Hodgkin's disease was marked by severe upper respiratory symptoms. Three of Reed's cases (431) occurred after pertussis. In a series of sixty cases of Hodgkin's disease cough, without gross evidence of pulmonary disease, was the complaint (309). Another case is cited in which chronic cough and "bronchial trouble" (63) preceded the onset.

It has been observed, however, that patients who begin to decline after a remission brought about by x-ray or mustard therapy frequently have upper respiratory disease; it is, therefore, equally reasonable to hypothesize that the association of Hodgkin's disease and upper respiratory disease at the apparent time of onset of Hodgkin's disease is due to the fact that Hodgkin's disease, as it becomes

sufficiently manifest to be recognized, predisposes the patient to the development of a secondary infection of the upper respiratory tract (243).

Typhoid fever, dengue fever and malaria are sometimes recorded in the medical history preceding the disease. Miller (382) cites the case of a patient who had had a tonsillectomy, diarrhea for twenty-five years, repeated attacks of gonorrhea, syphilis, malaria, and developed typhoid fever before the onset of Hodgkin's disease. One patient had had attacks of dengue fever 11, 10 and 8 years before admission for Hodgkin's disease, each time with inguinal and axillary adenopathy which subsided (121). Musser (398) reports Hodgkin's disease in a patient whose disease was preceded by typhoid and dengue fever.

Syphilis is rarely found in the history of the Hodgkin's patient. Gowers (210) reports three cases; and White and Senty (549), Davies (121), and Cabot (63) each report a case.

The association of Hodgkin's disease with tuberculosis will be discussed in the section dealing with etiology.

Smith (479) found the following conditions preceding the onset of Hodgkin's disease in 23 cases in children: 3 cases followed otitis media. 1 a furuncle of the neck, 1 mumps, 1 pertussis, 1 varicella, 1 trauma to the head and 16 occurred in apparently healthy children with no disease or accident which could be related to the onset. Smith further investigated the condition of the nose and throat in his series of children and found: septic tonsils in 4 children and carious teeth in 7 children, septic tonsils and carious teeth in 4 children and no abnormalities in 8 children. Smith concludes that Hodgkin's disease has no relation to preceding illness or foci of infection.

Goldman (200) reviewed 212 histologically verified cases and could find no predisposing factors in the environment, food, previous diseases or occupation. Burger and Lehman (58) in a series of 54 cases found that neither heredity, environment, occupation, nor diet appeared to play an important role in the development of Hodgkin's disease. Mills and Pritchard (384) could find no predisposing factors in a series of 20 cases. In a series of twenty-five cases, Cunningham (113) could find previous infection, tonsillitis and diphtheria, in only 2 cases.

An allergic history is reported very occasionally. A child who had been asthmatic since the age of 7 years developed Hodgkin's disease; a family history of allergy was recorded (497). Limper (330) cites the case of a child who had asthma, purpura, angioneurotic edema, measles and pertussis; Hodgkin's disease followed an attack of herpes zoster. Hodgkin's disease developed in a child who had longstanding eczema with itching (295). Barker (21) reports Hodgkin's disease in a 4 year old child who, during the year preceding the onset, had had furunculosis, scabies, eczema, impetigo, pyelitis and phlyctenular conjunctivitis. Seborrheic eczema, followed by mycosis fungoides and subsequently by Hodgkin's disease is reported by MacCormac (343). Hoster (248) describes the development of the disease in a 26 year old female who had had hives since childhood and whose paternal grandmother had allergic asthma.

Miscellaneous factors and conditions are reported in relation to the onset of Hodgkin's disease; mumps (221), erysipelas (470), intemperance, over-exertion, insufficient food, exposure to cold, mental depression, whooping cough, local irritation, childbearing (210) and status lymphaticus (426). Infectious mononucleosis (257), diarrhea of long standing (327), pneumonia (121), achlorhydria (509) and fibroadenoma of the breast followed by mastectomy (332) have been reported as bearing a chronologic relationship to the onset.

Markowitz (358) describes the case of a patient who received a blow on the neck 6 months before the onset of adenopathy in that area. The initial biopsy revealed a chronic inflammatory process with marked fibrosis and hyalinization. One year later the biopsy was indicative of Hodgkin's disease. Wallhauser (538) cites an additional 4 cases of Hodgkin's disease developing within a period of months following injury. Four cases reported by Goldman (200) contained a record of trauma in the area in which lymphadenopathy first occurred and Sternberg (493) mentions 3 cases previously reported by Dautwitz, 1 by Hersch, 1 by Kretschner and Block.

In one series of 100 clinic patients, "a history of non-specific tissue reaction and repair in the form of broken bones, chronic and acute infection, surgery, childbirth, etc. preceded the onset of the specific disease in many cases. In 20%, the relationship seemed to be direct and dramatic and in 42% suggestive or equivocal. In the remaining 38%, no history of trauma or infection that could be related directly or indirectly to the onset of the disease could be elicited" (245).

Hoster (243) has suggested that the length of time that the precipitating inflammatory process or tissue reaction precedes the onset of Hodgkin's disease is directly proportional to the subsequent chronicity of the disease, *i.e.*, the longer the interval, the more chronic the disease.

The authors of many case reports in the literature of Hodgkin's disease dismiss the past medical history as irrelevant. A remote personal and family history of tuberculosis is often sought, but other diseases or accidents which did not appear to have an obvious relation to the onset of Hodgkin's disease are often ignored. Nothing is known about the causative agent of this disease, if such an "agent" exists, and nothing about the incubation period or the individual predispositions which make for susceptibility.

If there are any predisposing factors in the past events or environment of the affected patients, it is possible that they may be most readily detectable in the young child who contracts the disease since the number of those events is necessarily limited by the age and since the environment with respect to certain factors is frequently under close supervision. The younger the child, on the other hand, the more likely it is to carry over prenatal influences, *i.e.*, disease transmitted through the placenta, or accident during pregnancy and labor. The interpretation of information obtained from the past medical history is made more difficult because the human memory is poor, most medical histories are not detailed or complete enough to be of value, many diseases go undiagnosed, and many incorrect diagnoses are made.

2. SYMPTOMATOLOGY

Painless, progressive enlargement of a lymph node or lymph nodes is the presenting symptom in approximately 79% of cases (200). Other symptoms in approximate order of frequency include: weight loss, loss of appetite, weakness, fever, pruritis, cough and dyspnea (58, 200, 330, 477, 571).

While the clinical course as a whole is characteristic, one of the distinguishing qualities of Hodgkin's disease is the variable week by week, month by month changing course of events (192). No patient develops all of the symptoms noted above; and rarely is there an orderly progression from one symptom to another. Spontaneous clinical remissions and exacerbations in the early stages are unpredictable. In many cases no definite correlation can be made between pathologic changes and symptoms; whenever possible, however, the relationship will be indicated.

Fever has been observed in a great number of cases, 31% (127) to 50% (23, 58) and may be of several varieties: (a) cyclic or relapsing, (b) continuous, (c) remittent or (d) intermittent. Pel-Ebstein fever is a dramatic type of relapsing fever which may be compared in form to Cheyne-Stokes respiration, the periods of apnea corresponding to normal or slightly subnormal temperature levels, and the periods of hyperpnea to the hyperpyrexic levels of 103 to 106° F. The cycle may last from 15 to 28 days and varies from patient to patient but is often of constant duration in the same patient. MacNalty (347) describes 5 cases with this type of fever; he also describes several cases of tuberculous adenitis with the same type of fever. Pel-Ebstein fever is not unusual in childhood (479); McCausland (367) found it in 3 of 13 cases in children. It is said to be rare in adult patients (200) although Burger and Lehman (58) noted it in 8 of 49 cases, Ziegler (571) in 2 of 120 cases and Baker and Mann (18) in 21 of 35 febrile cases. Barron (23) reports 3 cases in a series of 23. The intermittent type of fever, reaching levels of 100° to 101° F. daily, is the most common type observed (113, 200). The pulse rate is usually higher than would be expected from the temperature observed, unless the fever is due to secondary infection (200).

Remittent fever is considered by many investigators to be due in the majority of cases to intercurrent disease. In occasional acute cases of Hodgkin's disease with no demonstrable secondary invader the temperature curve appears to coincide with rapid septicemia-like dissemination of the disease.

An episode of fever may begin and end without obvious relation to adenopathy; the nodes of some patients, however, increase in size during the febrile period (267). Increased temperature is thought by some workers to be due to deep lymph node disease (129); others report that patients consistently without fever frequently have superficial involvement (18). Not infrequently, however, patients with both superficial and deep involvement die without fever (200). The ultimate cause of fever in Hodgkin's disease has not been determined; central necrosis of the node (200), autonomic nervous system disturbance (317) and reaction to an unknown pathogenic agent have been considered. Some suggest that the principle cause of the pyrexia observed is secondary infection; however, x-ray and other effective therapy in Hodgkin's disease usually cause a prompt decrease in fever (57). It has been noted by Creevy (110) that some cases of malignant nephroma have an intermittent type of fever.

Sweats are found frequently and are often associated with elevated temperatures especially if the fever is of the cyclic or remittent type.

Weakness and fatigue may be severe and often out of proportion to the extent of progression of the disease and to the degree of anemia.

Weight loss in some cases may be accounted for

by anorexia; the patient may lose weight, however, in spite of a normal appetite. The degree of weight loss is often of prognostic importance; loss of weight frequently precedes an exacerbation while weight gain usually follows successful palliative therapy.

Pruritis is reported in 3 to 85% of all cases. It may be associated with specific lesions of Hodgkin's disease of the skin, "id" reactions, or it may be without apparent local cause; the only skin abnormality that can be detected under these conditions is that produced by the scratching inflicted by the patient. Pruritis, like fever, is thought by some to indicate deep lymph node disease, particularly para-aortic involvement (129, 237). The treatment of enlarged nodes, wherever they are found, will aid in bringing relief from pruritis (102).

Dyspnea is found with moderate frequency and may be associated with the pressure-producing effects of enlarged mediastinal nodes, anemia or secondary bacterial infection of the lung occasioned by the decreased resistance of the patient.

Cough is caused by many of the factors responsible for the production of dyspnea. Pressure of enlarged mediastinal nodes on the recurrent laryngeal nerve (6) may result in "brassy" cough associated with hoarseness. Cough in Hodgkin's disease may be dry or productive depending on whether it is or is not associated with secondary infection. Charr (80) reports a very unusual case of uncomplicated massive pulmonary Hodgkin's disease in which hemoptysis occurred.

Pain, either localized or referred, is a frequent complaint. Bone pain, while not always as severe as in metastatic cancer, is nevertheless persistent and disabling (200). Pain due to bone disease is observed in the most frequent sites of bone involvement; and for this reason, back pain is a common symptom. Chest pain may accompany advanced intrathoracic disease; and paroxysmal abdominal pain due to the pressure of enlarged lymph nodes or to gastrointestinal involvement is not unusual. Mild neuralgias are said to be secondary to pressure on peripheral nerves, toxic products of the disease process itself or unknown foci of bacterial infection (52, 81, 538).

Although infiltration of the gastrointestinal tract is rare, complaints referable to this system are given by about 13% of patients (106). It is believed that many of the cases in which severe epigastric pain is present have erosions of the gastric mucosa due to avitaminosis (201). Pain in the left side of the abdomen may be due to perisplenitis; a dragging sensation in the left side of the abdomen may accompany the presence of a large spleen.

Neurologic symptoms are varied, ranging from mild neuralgias to symptoms referable to widespread and profound encephalomyelitic complications. The most frequent neurologic symptom complex is paraplegia. Rare neurologic symptomatology may be secondary to myelomalacia, meningitis or cortical involvement. Convulsions are rare (266).

Nausea and vomiting are not uncommon; diarrhea occurs less frequently. Grossly bloody stools have been noted; intestinal obstruction is rare. Jaundice is found in about 10% and ascites in about 18% of patients with hepatomegaly (266). Pleural effusion and edema of the ankles and legs are not uncommonly seen late in the course of the disease. Skin lesions of many types are encountered. Pathologic fractures are sometimes a troublesome complication associated with the osteolytic type of bone lesion. Hypersequestration of the formed elements of the blood accompanying splenomegaly has been noted in some cases and may result in the appearance of symptoms due to thrombopenia, leukopenia, and/or anemia.

3. TYPES

A majority of cases are said to progress through three stages: (a) a period of latency during which the nodes are enlarging without symptoms; (b) a period of progression and generalization during which symptoms of varying severity appear; (c) a period of cachexia which precedes the death of the patient (367, 538).

O'Brien (404) classified a series of 60 cases according to their duration: acute cases, a few weeks to a few months; sub-acute cases, a few months to 2 years; chronic or average cases, 2 to 6 years; and protracted cases, more than 6 years. Although acute cases are said to be rare, Cunningham (113, 114) found 3 among 25 cases; 1 was of 6 weeks duration.

Longcope (337) classified his cases in accordance with the degree of generalization of the disease and with respect to the chief localization, *i.e.*, mediastinal, abdominal, splenomegalic, osteoperiostic or gastrointestinal. Bersack (35) recognizes 3 clinical stages: localized, superficial multiple glandular and generalized. These 3 "stages" are observed in each of the histopathologic types proposed by this author (see P. 8).

Fabian (149) recognized 3 stages of the disease microscopically; a lymphatic hyperplasia, a polymorphocellular stage and a fibrous hyaline induration.

In analyzing the clinical course of 77 patients, Gilbert (192) formulated the following classification:

1. Average form (60% of cases).

Local adenopathy with later involvement of the mediastinum and the abdominal cavity; proceeds by successive bursts and remissions; finally becomes generalized with cachexia; accidents involving pressure on the abdominal viscera or infections increase the rate of progress of the disease.

2. Form with slow evolution (20% of cases).

Slowly progressive for years, even without treatment; subject to sudden bursts of activity; and may assume an acute character.

3. Rapid forms.

Few months duration; therapeutic efforts of little avail; and death due to visceral lesions or their complications rather than cachexia.

4. Acute forms (rare).

May run complete course during a period of a few weeks with high fever and rapid spread suggesting septicemia. In some of these cases all the nodes seem to enlarge at the same time.

The classification of Gilbert is useful in that it assists in indicating the prognosis of individual cases whose symptomatology may vary widely, and thus aids in therapeutic planning.

4. DIAGNOSIS

The final criterion on which the presumably unequivocal diagnosis of Hodgkin's disease rests is the cytopathologic appearance of diseased tissue.

In the average case a few simple rules should be followed: the choice of nodes of large size; the excision of more than one node if possible; the avoidance of irradiated nodes if others are accessible; the avoidance of surgical risk by the choice of the most innocuous site available; and the immediate preservation of the biopsied tissue in suitable fixative, followed by cutting, mounting and staining using approved technics (114, 267). A simpler method has been described in which lymph node imprints are made by bisecting the unfixed tissue, compressing it with a forceps and touching a slide with the cut surface. The latter is then rapidly fanned until dry and immediately stained (502). Since this method is relatively new, evaluation of its accuracy is not possible at this time.

In those cases in which the histopathology of the biopsy specimen is not diagnostic, Mankin (354) believes that the tissue culture technic makes possible an early diagnosis of Hodgkin's disease. Loseke and Craver (338) have employed aspiration biopsy in the case of lymphadenopathy or other foci of disease which for various reasons cannot be excised or are not visible to the eye. Morrison and Samwick (394) studied the sternal bone marrow biopsies of 22 cases of Hodgkin's disease and more than 100 cases of other blood dyscrasias. They observed that there was an increase in eosinophilic elements, reticulum cells and megakaryocytes and considered the bone marrow biopsy to be of aid in differential diagnosis.

A complete history, physical examination, blood studies, x-ray studies and observation of the clinical course are helpful in that they may contribute to a presumptive diagnosis (192). The basal metabolic rate may be of value since it is particularly high in some forms of Hodgkin's disease (243, 259, 455). When biopsy is impossible some workers have advocated the use of Roentgen radiation as a diagnostic test, reasoning that if the condition is Hodgkin's disease the tumors will subside quickly under the influence of radiation. Bone lesions, in which complete studies other than biopsy have strongly suggested Hodgkin's disease, are one example. The therapeutic use of roentgen radiation in mediastinal disease without biopsy may be dangerous since widening of the mediastinal shadow may be due to tuberculosis, aortic aneurysm and other causes; roentgen radiation is contraindicated in tuberculosis and aortic aneurysm (404). Moreover, rapid regression of mediastinal masses following roentgen radiation is not characteristic of Hodgkin's disease alone; bronchogenic and metastatic carcinoma may respond in a similar manner (96).

Gordon's finding (205) that intracerebral inoculation of rabbits and guinea pigs with suspensions of Hodgkin's lymph nodes produced a "characteristic" encephalitis led to the hope that the procedure would be of diagnostic value. The test is said to be positive in 65 to 75% of cases involving Hodgkin's nodes and negative in about 98% involving control nodes; the controls include normal and diseased lymph nodes of diverse origin (489). It was later discovered that a similar picture could be produced on occasion by normal bone marrow, spleen or leukocytes and that the false negative results among the Hodgkin's lymph nodes were found to occur in the case of lesions with few or no eosinophils. Investigation has recently been presented which suggests that the agent responsible for the production of encephalitis is concerned with the presence of human eosinophils (269). The Gordon test for this reason is non-specific (477, 489). Steiner (489) used the test in a series of 21 cases. Due to the widespread distribution of tissues giving the encephalitogenic reaction, Steiner stated that it was difficult to correlate this distribution with any one type of cell. While he agrees that the test is non-

specific, he believes that it is reliable in about 70% of cases.

The differential diagnosis of Hodgkin's disease includes giant follicular lymphoblastoma, myeloid and lymphatic leukemia, Cohnheim's subleukemic lymphatic leukemia, myeloblastic sarcoma, lymphosarcoma, reticulum cell sarcoma, metastatic carcinoma, Boeck's sarcoid, non-specific inflammatory adenopathy, certain fungus diseases, lymphogranuloma inguinale, typhoid fever, brucellosis, tuberculosis, syphilis and infectious mononucleosis (81, 192, 236, 455). The differentiation is possible in the great majority of cases by means of biopsy.

5. PROGNOSIS

It is very hazardous to prognosticate in the case of the individual patient with Hodgkin's disease. Patients with symptoms of severe disseminated disease may be treated and remain well for periods of 12 to 14 years (221, 268). Other patients presenting only localized involvement may die within 10 weeks (478). Acute cases appear; Sternberg (493) collected a number from the literature in which the duration was from 8 days to several weeks. No known factors give exact information concerning the life expectancy or degree of comfort during the course of the disease in a given individual (262). In a large series of cases, however, general correlations between prognosis and certain manifestations of the disease are possible. Some of the factors said to be associated with a good prognosis are:

1. Localization in one area (192, 268).
2. Localization in one area with early treatment (192).
3. Marked enlargement of external nodes before treatment.
4. Absence of leukocytosis or leukopenia (538).
5. Normal level of erythrocytes (129).
6. Females with Hodgkin's disease have a better prognosis than males (479).
7. Weight gain after x-ray.
8. Increase in split cholesterol and decrease in pure cholesterol (341).
9. "Patient showing osteoblastic metastases are in better condition and live longer" (273).
10. Rural rather than urban environments are conducive to a good prognosis (192).
11. Normal or nearly normal sedimentation rate (557, 245).

Factors said to be associated with a poor prognosis include:

1. Septic and Pel-Ebstein fever (337, 479).
2. Initial temperature elevation due to the disease.
3. Marked pruritis (129).
4. Splenomegaly (201).
5. Increase in pure cholesterol, decrease in split cholesterol (341).
6. "When the presenting symptom was other than adenopathy, the disease ran a more severe course" (200).
7. Cases in which symptoms of an acute infection immediately precede the onset of the disease are often rapidly fatal (268).
8. Parenchymal pulmonary involvement (268).
9. Patients with predominant localization in the abdominal cavity (201).
10. The development of gastrointestinal symptoms (388).
11. When the number of red blood cells "begins to fall more or less steadily" (129).
12. "Old age groups show malignant features" (35). Prognosis for children is serious (538).
13. A rapid sedimentation rate early in the disease is a bad sign (245).
14. Pronounced weight loss.
15. Marked lymphopenia (245, 337).

Jackson and Parker (264) state that they can correlate the histologic picture of affected nodes with the prognosis of the disease. Their histopathologic classification has been discussed in the section devoted to the pathology of Hodgkin's disease. Concerning prognosis they say, ". . .In broad terms, Hodgkin's paragranuloma is a comparatively benign condition, occasionally progressing to Hodgkin's granuloma. . . . Hodgkin's granuloma is characterized by the most protean manifestations, is usually though by no means invariably fatal within a few years, and on rare occasions progresses to Hodgkin's sarcoma. . . .Hodgkin's sarcoma behaves as a highly malignant, comparatively localized tumor, rapidly resulting in death."

Goldman (200) and Mills and Pritchard (384) find no relation between the histology of the lesions and the prognosis of the disease. Slaughter and Craver (477) assert that no histopathologic classification is possible since nodes are in all stages of pathologic development in the same individual at one time. Of 14 cases diagnosed as "Hodgkin's sarcoma," 5 lived more than 3 years. They believe that the prognostic factors in Hodgkin's disease depend upon the location and extent of the lesions.

Cunningham (113) states that many of the early and late histologic variations can be seen in one gland or its group.

A normal level of lymphocytes in the blood and a large number of lymphocytes in the lesions are considered to have a favorable prognostic significance. Rosenthal (442) found that the duration of life after the onset of Hodgkin's disease was pro-

portional to the "predominance, subordination or absence of lymphocytes and lymph nodules in the affected nodes." In a series of 63 cases, the average duration of life for patients with these 3 characteristics was 4.35, 2.29 and 1.14 years respectively. On postmortem examination, a marked decrease in the number of lymphocytes and lymph nodules was evident in the spleen and lymph nodes in all cases with or without radiation. This was true whether the organ was involved by the disease process or not and was explained by the "indirect action of the products of tissue destruction entering the blood stream." Four instances of Hodgkin's sarcoma were seen in those cases in which the number of tissue lymphocytes were greatly reduced. Yates (565) asserted that an abundance of lymphocytes about the local lesions and in the blood stream indicated a more competent defense. He considered the lymphocyte as a possible storehouse of antibody, a concept which remains controversial. In studies of tumors, Tyzzer (517) presented evidence that the lymphocytes were important in the defense against carcinoma and that there was a relative increase in the numbers of lymphocytes during the retrogression of carcinoma and a relative fall during the period of active growth. Tyzzer observed that it is possible to lower the resistance of immunized animals to tumors by exposure to x-ray, an effect attributed to the destructive action of these rays on the lymphoid cells. Wiseman (559), on the other hand, studied 31 cases of Hodgkin's disease which had not been given Roentgen radiation and found no correlation between levels of lymphocytes and the activity of the disease, except during phases of extreme toxemia.

There are many suggestions that sex plays an important role in the prognosis of Hodgkin's disease. Not only do females appear to be less susceptible, but also they are said to live longer as a group after having acquired the disease. In a study made by Epstein (145), the average duration of life of 104 males after the onset of the disease was 2.3 years, while the duration of 63 fatal cases in the female was 3.4 years. Three-quarters of the females in this group of cases lived more than 3 years after the disease began and only half of the males. More than 50% of the females survived for over 5 years and only 10% of the males. Nearly 20% of the women and only 5% of the men were still living after 10 years. The age of onset did not differ significantly in the males and females in this series. Epstein notes that "During the first ten years of life, when the female physiology most closely resembles that of the male, 37.5% of the females died in less than three years." Between the ages of 30 and 50 the mortality during the first 3 years of the disease decreased to about 8% and was observed to ascend "as sexual activity decreased." This author did not find a similar pattern in patients with lymphosarcoma. In a study of 477 lymphoblastomas including 173 Hodgkin's patients, Minot and Isaacs (389) found no appreciable difference between the sexes in regard to duration of the disease.

It is believed that women with Hodgkin's disease have a decrease in ovarian activity and that about one-half of the cases become manifest during periods of physiologic amenorrhea, particularly during pregnancy (190) or at the time of the menopause (389).

Once the disease is established, the effect of pregnancy on the prognosis is variable. Rapid enlargement of the nodes during gestation has been observed (81, 295). Very rapid advance of the disease following delivery is reported (81, 122, 295). On the other hand, many women have borne children, some more than once, without demonstrable ill effect (192, 201, 268, 380, 388, 438, 455). Nevertheless, it has been suggested that women with Hodgkin's disease be advised against pregnancy (101, 268).

It is difficult to present accurate data indicating the duration of Hodgkin's disease since it is impossible to establish the time of onset even within a period of months. One group of authors estimates the duration of the disease from the beginning of symptoms, others from the time of biopsy and still others from the beginning of treatment. Although the time of biopsy and the beginning of treatment are accurately recorded during the course of the disease, figures for the duration of life based on these dates are obviously distorted. Chronic cases may live for years without diagnosis; economic conditions and lack of medical facilities may delay the time of accurate diagnosis for significant periods. In addition, the protean symptomatology of Hodgkin's disease makes it hazardous to fix the onset by means of possible coincidental complaints. For the reasons mentioned the problems involved in the establishment of good criteria for judging the duration of the disease make all figures less valuable than might be hoped; the individual choice of criteria exercised by each author makes comparisons almost impossible. In addition, the case series themselves vary in respect to the percentages of slow and rapid forms, the degree of progression of the disease at the beginning of therapy, the age of the patients, the method of treatment used and the ratio of the sexes (192).

Wallhauser (538) studied survival figures re-

corded in the literature before 1932 and found a range of 17 to 37 months. He concluded that the average duration of life following the onset of the disease is slightly more than 24 months.

6. CAUSE OF DEATH

About 50% of patients with Hodgkin's disease die in the toxic state attending multiple visceral invasion or terminal disease associated with secondary infection (18, 58, 88). Although this is encountered more often in acute cases, many of the chronic forms may suddenly develop symptoms of acute toxemia and die. Pressure on vital structures, particularly in the mediastinal region is said to be responsible for about 35% of deaths (268).

Following Sternberg's report linking tuberculosis with Hodgkin's disease, the relatively frequent occurrence of deaths due to tuberculosis has been noted (322, 346, 408, 471, 495). With the decrease in incidence of tuberculosis, association of the two diseases has shown a quantitative decrease (311).

The secondary effects of radiation therapy, including pulmonary fibrosis, myelophthisis and agranulocytosis, are said to account for a significant number of deaths in Hodgkin's disease. Improvement in radiotherapeutic technics and more careful laboratory studies are said to have cut down the mortality from this source. The use of new chemotherapeutic substances may reduce the amount of radiation necessary and thus further diminish this source of danger.

A large number of patients die with general bone marrow exhaustion and aplasia. Some of these exhibit evidence of rapid destruction of cells introduced by transfusion.

D. Laboratory and Biologic Studies

1. BLOOD STUDIES

Hemoglobin and red blood cells.—Patients with Hodgkin's disease may have a normal hemoglobin and red blood count during the early stages of the disease. During the periods of exacerbation and as the disease advances a mild normochromic or microcytic anemia is usually present. Occasionally a macrocytic anemia is noted with or without achlorhydria. Such cases rarely show a sustained response to liver (217). As the patient begins to fail, the anemia frequently becomes progressively more severe and in the terminal stage becomes refractory to all treatment including transfusions.

The erythroid series in the bone marrow shows little more than moderate hypoplasia (217, 518) unless the case presents the type of complication which, of itself, produces characteristic bone marrow changes. For example, massive involvement of the liver may produce erythroid arrest at the megaloblastic level.

White blood cells.—Changes in the white blood cell count of patients with Hodgkin's disease, though often marked, are said to be neither constant, typical nor diagnostic (201, 267, 297, 559, 570). Early in the disease the white count may be normal (201, 267, 444), slightly decreased (51, 200, 259, 336) or slightly increased (50). As the disease advances, the count may remain normal but is usually somewhat increased. Leukopenia is infrequently found in uncomplicated, untreated Hodgkin's disease (18, 58, 381) but is said to be present more frequently in childhood (297, 479), in late stages of the adult disease (444) or in association with Pel-Ebstein fever (201, 297). Leukopenia has been reported in as many as 12% of treated and untreated patients with Hodgkin's disease. When the leukopenia is due to Hodgkin's disease rather than to radiation or intercurrent disease, successful x-ray therapy may be attended by a rise in the white blood cell count (144). During the course of the disease, leukocytosis (in one case as pronounced as 169,000 cells per cu. mm.) is occasionally seen. There are a few reports of lymphatic leukemia and Hodgkin's disease occurring in the same patient (234, 540, 543). A definitely elevated white blood cell count in Hodgkin's disease is said to indicate that the disease is widespread (259, 559). Rarely is there constant correlation between the clinical picture and the white blood cell count (267).

An absolute increase in neutrophils is observed when there is a leukocytosis and frequently observed when the white blood cell count is normal (192, 201, 559). The occurrence of lymphocytosis early in the disease has been noted by Bunting (50); this phenomenon has not been observed by Wiseman (559) and others (251). As the disease progresses an absolute lymphopenia is observed by most investigators. The number of circulating lymphocytes may increase during a beneficial response to therapy but usually does not return to a normal level (251, 297). The lymphocytes seen are normal, mature cells in contrast to the young and abnormal forms seen in diseases characterized by lymphoid hyperplasia (251, 559).

The number of monocytes in the circulating blood is frequently increased (31, 192, 221, 297, 559) and in some cases greatly increased (262). The level of monocytes is said to be consistently elevated in those patients whose blood smears have been specially stained so that the monocytes are clearly differentiated from other white blood cells (559). The monocyte-lymphocyte ratio is higher than normal in more than 90% of cases (559).

When it can be accurately followed, the monocyte-lymphocyte index is an excellent prognostic test (251, 570).

Despite the popular opinion that eosinophilia is typical of Hodgkin's disease (287), these cells are present in increased numbers in only 15 to 20% of cases (58, 92, 200, 506, 518, 559). Levels above 100,000 eosinophils per cu. mm. of blood are said to be found in rare cases (350, 497). The significance of the eosinophilic reaction in Hodgkin's disease is not known but has been attributed to a special chemotactic substance present in the affected lymph nodes (50, 311, 334), necrosis of the nodes (236), reaction to x-ray therapy (192), splenic involvement (396) and an allergic response (497).

The total number of circulating platelets in untreated cases is usually increased especially early in the disease, often to levels of 3.5 million per cu. mm. Low platelet counts associated with hemorrhagic and purpuric diatheses are encountered rarely as the presenting symptom of the disease (245, 474). They appear to be the result of overtreatment with x-ray (201, 372), terminal disease or hypersequestration of platelets by the spleen (245). Frequently the blood smear contains abnormally large platelets with pseudopod formation; earlier workers believed these to be masses of megakaryocytic protoplasm (49, 564). Megakaryocytes have been described in the blood stream in small numbers; they are said to be constantly accompanied by total white blood cell counts of at least 25,000 and their presence is considered to indicate that the bone marrow is under severe strain (385).

Aspiration of the sternal marrow is not considered to be a diagnostic measure of positive significance since Sternberg-Reed cells are rarely found (201). An increase in monocytes and in fibrous tissue with hypoplasia of the erythroid and myeloid elements has been described in patients with advanced Hodgkin's disease. Although the Hodgkin's cells themselves are rarely seen, monocytosis and increased fibrosis in the marrow with an occasional increase in plasma cells are considered to represent involvement of that organ (251, 570). Although qualitative cellular changes in the marrow are rare, there may be a left shift in the erythroid series in the presence of a peripheral anemia. Examination of sternal smears from 91 patients indicated the following general changes (201): (a) a shift in the leukocytic series to the right with marked toxic granulations; (b) an increase in young myeloid eosinophils; and (c) an increase in the monocytic series.

Although the changes in the blood and bone marrow are not specific, the characteristic blood picture, when seen, is suggestive. Wiseman (559) states "... Given a blood study that shows a lymphopenia with a high monocyte-lymphocyte index with normal total white blood cells, a mild neutrophilia and any increase in eosinophils, one would appear to be justified in suggesting the possible diagnosis of Hodgkin's disease on the basis of the blood examination alone...I have observed no other disease, save an occasional case of tuberculosis, that gives this blood picture."

All conclusions concerning the blood and blood-forming organs of patients with Hodgkin's disease must be drawn with great reservation. Roentgen therapy may profoundly alter the activity of hemopoietic tissues, and for this reason, one group of investigators finds it is difficult to differentiate the changes brought about by the disease from those produced by therapy.

The erythrocyte sedimentation rate.—The usefulness of the red blood cell sedimentation rate in following the course of many diseases both acute and chronic is well known. The precise significance of the change in sedimentation rate is not understood. It has been suggested that alteration indicates metabolic changes with results from nonspecific destructive disease (401). Most patients with Hodgkin's disease have an elevated sedimentation rate during periods of disease activity, with return to a more normal rate following effective palliative therapy and during periods of spontaneous remission. It is therefore apparent that the test is useful in following the course of the Hodgkin's patient and may serve as a guide in therapy (245, 251, 557). The sedimentation rate may be normal during the early stages of chronic Hodgkin's disease of long duration (570).

An exception to this observation is the behavior of the sedimentation rate of Hodgkin's patients treated with colloidal arsenic. In several cases the drug was observed to lower the sedimentation rate without influencing the course of the disease; when the arsenic was withdrawn, the sedimentation rate rose to its original elevated level. This divergence from the usual parallelism of the sedimentation rate and the clinical course of the disease has not been explained (122, 243, 445).

In 1937, Koster (305) and again in 1940 Feldman (152) noted that, in the case of most individuals, the sedimentation rate of erythrocytes in drawn blood decreases after the first few hours and reaches very low values at the end of 24 hours. On the other hand, patients with malignant tumors, Hodgkin's disease and those receiving certain drugs (potassium iodide, bismuth, salvarsan, aminopyrine,

lipiodol, perabrodil, oral tetragnost, sulfanilimide, sulfapyridine) had a sedimentation rate which remained constant or even increased over the 24 hour period. This behavior was attributed to a shift of potassium from the plasma into the red blood cells. The conclusions concerning variations in the 24 hour sedimentation rate were drawn from a study of large numbers of cases, as indicated below:

Abnormal Sedimentation Behavior	Normal Sedimentation Behavior
1. 106 of 112 cases of proven cancer.	1. 100 Normal
2. 14 of 14 cases of Hodgkin's disease	2. 60 patients with diverse disorders other than cancer or Hodgkin's disease.

Mendel and Korenberg (378) restudied the 24 hour sedimentation phenomenon, and while their results were not as clear-cut as those of the original workers, a statistically significant difference between the blood of patients with cancer and the blood of controls was observed. Apter, Hull and Adams (10) varied the temperature at which the blood was stored, analyzed the resulting rate changes and could not confirm the claims made for the 24 hour test. They conclude "...The test is empirical and cannot be correlated with any known differences between the blood cells or plasma of persons with or without cancer."

The value of the 24 hour sedimentation rate test in the diagnosis of Hodgkin's disease will depend upon a confirmation of the results described above and a demonstration of its specificity.

Miscellaneous blood studies.—Bleeding and coagulation time and clot retraction are usually normal. Fibrin is said to be increased during febrile periods, paralleling the concomitant polymorphonuclear leukocytosis.

Luden (341) made weekly determinations of blood cholesterol in one patient for two years and concluded that "after treatment with radium there is a fall in pure cholesterol and an increase in split cholesterol. When the blood shows the opposite, new nodes will appear." Further remarks by Luden (341) on the subject of cholesterol may be of interest. "The influence of the chemical composition of food on the chemical composition of blood in increasing or diminishing the amount of cholesterol is clearly demonstrated. A diet which increases the blood cholesterol coincidentally weakens the lymphoid defense." Luden reported that in a small number of cases x-rays increased the lymphocyte count while it lowered the cholesterol of the blood.

Recent studies have cast serious doubt on the hypothesis that the amount of blood cholesterol varies with the ingestion of cholesterol-containing foods. Moreover, the liver, which is presumably the most important organ of cholesterol metabolism, is involved so frequently by Hodgkin's disease that variations in the level of this compound are not surprising. Recent workers, furthermore, have failed to confirm Luden's observation of a change in blood cholesterol with the onset of remission (122).

Blood lipase values have not been extensively studied but there is a suggestion that the levels are low in patients with leukemia, pernicious anemia and Hodgkin's disease. Twort and Archer (512) believed that certain diseases, especially those of virus etiology, which excite a mononuclear response are accompanied by a lowering of blood lipase, and that, when immunity to the disease has become established, the lipase content of the blood rises again. Variations in blood lipase have been observed in many cases in which cell proliferation or cell necrosis is taking place (474). This test may, therefore, have no specific significance in Hodgkin's disease.

The iodine number was determined in 11 cases of Hodgkin's disease; it exceeded the normal by 2 or 3 times, the variation from the normal being directly proportional to the duration of the disease. Roentgen therapy had no definite effect on the iodine number in the cases studied (348).

Vitamin C balance experiments were performed in the case of 6 patients with Hodgkin's disease. The "actual deficit" was removed in 2 or 3 days by large amounts of vitamin C given intravenously. The amount administered to each patient subsequently was lowered in proportion to the excretion. The "actual deficit" required between 1,000 and 3,000 mgm. although very severe cases required as much as 5,000 mgm. for saturation. The daily utilization of vitamin C, *i.e.* the "current deficit" after saturation of the "actual deficit," amounted to approximately 500 mgm. depending on the severity of the disease (530).

Serum protein components.—The serum albumin may be normal but is usually decreased; the globulin is said to increase with fever and may return to normal terminally. The A/G ratio may be normal during afebrile periods and may be decreased when the temperature becomes elevated (81).

Nitshe and Cohen (402) studied serum protein levels in 26 cases of Hodgkin's disease and found 15 with albumin values below the lowest observed in the normal group. The serum globulin level in 23% exceeded the highest value found in the normal group. There was no statistically significant change in the total protein level.

Thirty-three analyses of serum from patients with Hodgkin's disease were made in order to deter-

mine the electrophoretic patterns (446). None produced a pattern peculiar to Hodgkin's disease. Three types of curves, designated A, B and C, were, however, obtained and each curve could be more or less readily correlated with the clinical state of the patient. Thus the A curve, a normal pattern, was obtained from patients in the best state of nutrition. The B curve, characterized by elevated alpha globulin components, was produced by terminal patients, those who were cachectic, anemic, febrile and edematous. And finally, the C group, characterized by elevated gamma globulins, was furnished by patients intermediate between the 2 others, not terminal but definitely more ill than those in class A. Comparison of findings with those obtained from sera of tuberculosis patients failed to show any parallelism between tuberculosis and Hodgkin's disease. In the former, the alpha globulin rose early in the course of the disease, while in the latter illness, a rise of the same fraction occurred terminally. In tuberculosis the increase in gamma globulin appeared related to immunologic processes, while in Hodgkin's disease no such conclusion could be made.

Serologic studies.—No complement fixation or other serologic test has been devised for Hodgkin's disease. Stewart and Doan (495) find a high precipitin titer for avian tuberculophosphatid in the serum of many patients with Hodgkin's disease. The average titers in control cases are lower.

When syphilis is not present in Hodgkin's disease, the Wasserman reaction is negative although, infrequently, doubtful and false positive reactions have been reported.

The serologic studies described by M. S. Hoster (252) were designed to aid in determining the nature of Hodgkin's disease. The collodion particle agglutination test, the complement fixation test, the red blood cell agglutination test and the "cold" hemagglutination test were employed in an effort to demonstrate immunologic specificity.

The six sources of "hypothetical antigen" used in serologic studies included: (a) tissue extracts, (b) transudates, (c) high gravity centrifugates of tissues and (d) high gravity centrifugates of transudates obtained from Hodgkin's and control patients, (e) supernatant fluids from Hodgkin's cells in tissue culture and (f) extracts of fertilized chicken eggs inoculated with Hodgkin's tissue suspensions. The four sources of "antibody" included: (a) sera from patients with Hodgkin's disease, (b) the supernatant fraction of Hodgkin's tissue extract high gravity centrifugation, (c) sera from rabbits inoculated with the pellet fraction of Hodgkin's tissue extract high gravity centrifugation and (d) sera from rabbits inoculated with supernatant fluids from Hodgkin's cells in tissue culture.

In 10 experiments including the study of 373 samples of Hodgkin's sera and 240 samples of control sera tested against 96 "antigen" preparations, the collodion particle agglutination test yielded equivocal or negative results. A total of 27 "antigen" preparations were tested against 221 Hodgkin's and 132 control sera by means of the complement fixation test. The results were negative.

A hemagglutination factor for rabbit red blood cells, found in tissues of Hodgkin's patients, was not specific for this disease since the factor was also found in tissue of control patients. "Cold" hemagglutinins in Hodgkin's sera were not demonstrated in titers higher than those present in the sera of normal individuals.

A study of blood groups, observed in patients with Hodgkin's disease, by A. Rottino (445) revealed a distribution suggestive of the random sampling obtained from any heterogenous group of individuals. The serologic results described are considered preliminary.

2. OTHER LABORATORY STUDIES

Urine.—Unless there is infiltration of the kidneys or pressure on the excretory urinary tract, the urinary changes are those which would be expected in a chronic, intermittently febrile disease. Urine output is reduced in severe forms but is normal in the majority of the remaining cases. Castex quoted by Chevallier and Bernard (81) reports a slight but permanent polyuria. Many patients complain of nocturia especially during exacerbations of the disease. Albuminuria is frequently seen but is moderate and of the type observed in febrile disease. If albumin is present in the urine in large quantities, the kidney may be specifically involved by the Hodgkin's disease process, by amyloidosis or by another disease process. In summary, renal function is unimpaired unless the kidney is specifically involved extrinsically or intrinsically by the disease or by another disease. Urobilinuria is found in a great number of cases. Indican in the urine has also been reported. Glycosuria during febrile periods may be observed and is usually transitory. Following Roentgen therapy, an excretion of nitrogenous compounds including uric acid occurs. Ehrlich's diazo reaction may be observed in the generalized and febrile forms of the disease (81).

A Bence-Jones-like protein has been found in the urine of one case of Hodgkin's disease by Galloway (184). At autopsy the kidneys were found to be involved by the Hodgkin's process.

Spinal fluid.—Spinal puncture is not performed

in patients with Hodgkin's disease unless suggestive neurologic signs appear. The pathologic anatomy of lesions of the central nervous system often determines the type of spinal fluid changes which one may expect. If the lesion involves the spinal cord, block may occur and characteristically the pressure changes below the level of the block are indicative of abnormal spinal fluid dynamics. Spinal fluid protein is usually increased if metastases have developed in the cranial cavity or spinal column. Cell variations depend on the type and extent of meningeal reaction, and in most cases there is an increase in the number of lymphocytes. When invasion of central nervous system tissues has occurred, the results of the colloidal gold test are similar to those observed in the case of any tumor of the central nervous system (538). In cases in which myelitis is present, there often appears "a midzone curve suggestion of syphilis or early multiple sclerosis. Under x-ray therapy, the curve has usually flattened out or shows a tendency to less marked midzone rises" (266). There is no spinal fluid change which by itself is characteristic of the Hodgkin's disease process.

Gastric juice.—There has been little systematic investigation of gastric secretion in Hodgkin's patients. When gastrointestinal symptoms appear, there is often an accompanying hypo- or achlorhydria (538). Brach (43) reports that, in a case of Hodgkin's disease in which pruritis was present, a test of alimentary hemoclasis (ingestion of 200 cc. of milk) produced a marked response, the calcium-potassium quotient showing an 8% decrease. Brach interprets this reaction as a "parasympathicotonic disturbance."

Basal metabolic rate.—The increase in basal metabolic rate is proportionate to both the extent (259) and the activity (243) of the Hodgkin's disease process. When the disease is localized, the basal metabolic rate is not significantly altered and therefore is not of diagnostic significance (325). The metabolic rate is said to be especially high when abdominal organs are the principle site of the disease.

Following roentgen therapy, the basal metabolic rate of radio-sensitive patients usually returns to near-normal or normal levels. The relationship between the basal metabolic rate and the extent of the disease process may be a variable one. When repeated determinations are made and evaluated concomitantly with other laboratory data, they may be very useful in indicating the degree of improvement or relapse and the rate of progress of the disease.

Krantz (306) investigated 30 patients with lymphoblastoma including an unspecified number with Hodgkin's disease and found widely disseminated disease when the basal metabolic rate was +20% or more.

Skin tests with tuberculin.—Patients with advanced Hodgkin's disease characteristically fail to react to tuberculin. This anergy is seen occasionally in association with active tuberculous lesions (409). Large doses of the specific protein material frequently fail to call forth a local response (487), and when a positive test occurs, it is usually minimal and the next larger dose rarely causes a significantly greater reaction. In general, patients with lymphomatoid diseases are said to show a decreased sensitivity to tuberculin; there are fewer positive reactions among the Hodgkin's group of patients than among those with other lymphomas (409). Some clinicians feel that a strongly positive tuberculin test in a patient with Hodgkin's disease is presumptive evidence of active tuberculosis (262). A positive tuberculin test, however, may occur early in the course of the disease without demonstrably active or advanced tuberculosis (243).

Avian tuberculin has been used in order to elucidate a possible relationship between Hodgkin's disease and the avian mycobacterium. Some authors report fewer reactions with avian than with human tuberculo-proteins (487), while others report the opposite finding (409). In any case, the differences between the two types appear to be too small to be significant, and it is unlikely that there is any practical or theoretical advantage in the substitution of avian tuberculin for human tuberculoprotein.

Occasionally the tuberculin test becomes positive after effective roentgen therapy (262, 409) and improvement in the health of the patient. Roentgen therapy, however, may have a deleterious effect on "silent" tuberculous lesions and cause them to become active.

It has been suggested that "either Hodgkin's disease desensitizes its victims to tuberculoproteins or Hodgkin's disease occurs normally in persons in whom development of sensitization to tuberculin is impossible" (487).

Other skin tests.—When brucellosis complicates Hodgkin's disease and sensitization has been established to the former, the brucellin or brucellergen test is usually positive except during the terminal stage of the disease.

Many attempts have been made to develop a skin test which is specific for Hodgkin's disease. All efforts which have been directed toward the production of an antigen for the skin testing of patients with lymphomatoid diseases have failed.

The experiences of Chapman (75) and Gordon, Gow, Levitt, and Weber (208) are typical. Chapman removed nodes from an untreated patient with Hodgkin's disease, extracted them with saline, centrifuged them and added 0.3% tricresol to the resulting cloudy supernatant fluid. One-half the supernatant was incubated for one hour at 60° C. on 2 successive days. Eleven irradiated patients with Hodgkin's disease were tested for skin sensitivity with this extract. Results were negative in all but 1 case that showed a transient reaction at 24 hours. The patients also failed to react to similarly prepared and treated lymph node extracts from a case of lymphosarcoma. Gordon and associates (208) injected 20 cases of Hodgkin's disease and 10 controls with raw extracts of Hodgkin's nodes intradermally with negative results. When they used nodes which had been dried *in vacuo,* 3 caused variable local reactions. The controls were uniformly negative.

No antigen for skin testing has been developed to which patients with Hodgkin's disease react as a group. If such an antigen exists in diseased tissues, methods of preparation used to date have either altered its antigenicity during preparation or failed to extract it in sufficiently concentrated form to incite an observable response. With the recent preparations of ultra-centrifuge purification products from surgical and postmortem specimens of Hodgkin's tissues (246), the opportunity may arise to re-evaluate the question of skin testing in Hodgkin's disease. These, as well as extracts from tissue cultures of living Hodgkin's cells (212, 246), may be possible sources of a more potent and biologically active material.

E. Treatment

1. ROENTGEN RADIATION

An effective treatment of Hodgkin's disease has been earnestly and actively sought for many years. Roentgen radiation was early recognized to be a potent therapeutic measure and remains the treatment of choice for localized Hodgkin's disease. More advanced and widespread disease may respond less effectively to roentgen radiation alone. The recent use of nitrogen-mustard therapy with roentgen radiation of selected specific areas appears to be the most effective method of treatment for patients with disseminated Hodgkin's disease.

A few clinicians believe that there is no evidence that roentgen radiation influences the average duration of life in patients with Hodgkin's disease (23, 404). This point of view, however, is exceptional. Most workers have reported that x-ray restores the patient to comparative health in many cases and lengthens life.

The goal which must be achieved and the problem which must be overcome by roentgen therapy varies with the condition of each patient, and radiologists themselves differ in their general expectations and criteria of satisfactory therapy. "The great diversity of lesions found in this disease precludes the establishment of any one routine of therapy and leads to the variety of technics used and the results obtained" (99). The paucity of "cures" or long-term arrest of the disease following roentgen radiation has led many to believe that only temporary palliation is possible; this group of workers aims merely at the relief of symptoms and prolongation of life. Others take a more vigorous stand and attempt to achieve prolonged remissions equivalent in a sense to "temporary" clinical "cures" (192, 268). Finally there is still another group of radiologists which believes in strong irradiation of specific foci of the disease, especially if the disease is localized. In this instance the aim is complete and permanent eradication of the disease.

In our present state of knowledge there seems to be little question that "persistent, early and thorough x-ray therapy" is indicated when the diagnosis of Hodgkin's disease is made (437). The palliative effectiveness of the technic has been repeatedly illustrated in bringing even the apparently moribund patient "back from the brink of the grave" (102).

Boldness in the application of irradiation must be modified in the face of certain complicating clinical findings. In general, the principal contraindications to roentgen radiation are the following:

a. "Acute forms" of Hodgkin's disease (192).

b. Active tuberculosis in regions where roentgen therapy is to be applied (192, 268).

c. Renal insufficiency (192, 268).

d. Previous deleterious effects of irradiation, especially impairment of the integrity of the skin (192).

e. Toxic depression of bone marrow function with severe depletion of one or more of the formed elements of the blood.

During the course of roentgen therapy the blood count must be carefully and repeatedly studied; when signs of diminished leukogenesis become obvious, all roentgen radiation procedures must be suspended until the bone marrow recovers sufficiently to justify continuation of therapy.

The application of roentgen therapy to superficial lymph node groups is a relatively simple pro-

cedure followed in most cases by excellent local results. When deep nodes and viscera are to be irradiated, the results are more variable. It has been postulated that early prophylactic irradiation of a focus may abort a serious train of symptomatic and pathologic events (192). Before roentgen therapy is used, thorough investigation of the patient and his symptoms is necessary: (a) to evaluate his probable tolerance, (b) to recognize all possible sites of the disease, (c) to uncover any contraindications to irradiation and (d) to determine the degree of chronicity of the disease (101).

Usually the sites of the disease responsible for the predominating symptoms are irradiated first (101, 130, 201). Gastrointestinal symptoms, fever, weight loss, general debility, a high leukocyte count and pruritus often indicate the need for abdominal irradiation (102, 129, 268, 388, 477). Exposure over this area is often followed by serious depression of the bone marrow and must be performed with care.

Hodgkin's disease of the lungs may be very radiosensitive, yet partly because of the depth and character of the tissue bed the lesions are not so easily controlled by irradiation as are some other manifestations of this disease (105). Large effusions may require thoracentesis before roentgen ray therapy is begun. Single massive doses are avoided (560), especially in the presence of large mediastinal nodes; following excessive radiation these may undergo rapid necrosis which is said to result in a severely toxic effect on the patient (268). Care must be exercised to prevent irradiation pneumonitis (5). A majority of the patients who receive judicious mediastinal roentgen therapy show a favorable response (101, 560).

Pain, deformity or roentgenologic evidence of bone involvement is indicative of the need for irradiation of the area involved. Roentgen therapy is said to halt the pathologic process, with apparent return of the bone to normal in some cases. In others, bony lacuna may persist, or sclerosis and hyperplasia may result (192). Paraplegia is often effectively treated by irradiation of the involved vertebra. If roentgen therapy is given early, complete disappearance of the paraplegic symptoms may result (102, 380, 477). It has been suggested that prophylactic doses of roentgen radiation be given at the proper spinal level when herpes zoster appears in order to forestall the possible development of paraplegia (200).

Logical suspicion of the involvement of any organ or region justifies the administration of irradiation carefully given with regard to all pertinent factors. The brain (59), eye (15), pharynx (266), heart (183), pelvic organs (538) and bladder (538) have been treated with more or less success during life.

The technic of application of roentgen radiation remains a controversial subject. The quantity of irradiation, the time and distribution of treatment, the penetrability of the rays as well as the sites of application must be considered. The most important radiotherapeutic technics used in Hodgkin's disease include:

a. Local high voltage x-rays in fractionated tissue-destructive doses.
b. Local moderately high voltage x-rays in palliative doses.
c. General body irradiation with or without local destructive x-ray.

For localized disease, Slaughter and Craver (477) advocate the use of heavy irradiation in fairly large single doses. These workers use a. 200 to 250 kv. machine with a 0.5-1.5 mm. copper filter and large rectangular portals, giving 200 to 400 r daily and up to 600, 800 or 1,200 r during a given course. In the treatment of the recurrent solitary nodes, small circular portals and high dosage are used. Slaughter and Craver do not advocate prophylactic irradiation.

O'Brien (404) advocates 200 kv. and a total fractionated dosage which may reach 2,000 r in a single course. Friedman (178) uses 180 kv., 4 ma. with 0.5 mm. copper and 1.0 mm. aluminum filters at 50 cm. distance. Higley and Hauser (237) prefer high voltage roentgen rays given in multiple small doses. Jenkinson (273) attempts to destroy involved nodes with one roentgen ray treatment. Gilbert (192) recommends the use of a large destructive dose because he finds that radioresistance is required by patients who have been subjected to repeated small doses over a long period of time. He administers large doses using 170 to 200 kv. with a filtration of 0.5 mm. of copper and with a focal distance varying from 35 to 60 cms. according to the site and volume of the masses to be irradiated. Fractional doses at short intervals are preferred, and the course is repeated only if there is a recurrence or if the masses have not regressed sufficiently. Gilbert irradiates obviously involved areas as well as those regions that offer only presumptive evidence of involvement. If the patient continues to have symptoms despite the recession of adenopathy, Gilbert irradiates the paravertebral, retroperitoneal and para-aortic nodes and the spleen. The technic of Gilbert is used by many others

including Jackson's group at the Boston City Hospital (268).

Comparatively small doses of roentgen rays are often advocated by those who believe that Hodgkin's disease is invariably and rapidly fatal and that roentgen rays should never be used in doses that risk impairment of the general condition of the patient. In line with this reasoning, Desjardins (128) recommends small and less penetrating doses, emphasizing the relative radiosensitivity of most Hodgkin's lesions (130). "The use of large doses makes further treatment of the recurrences impossible, or if attempted, there is little or no effect due to radio-resistance." However, he concedes that, if the pathologic process is confined to one group of nodes, maximum dosage may be justified. Desjardins applies rays of 130 to 140 kv. strength through a 4 to 6 mm. aluminum filter for superficial, mediastinal and retroperitoneal nodes; if the nodes are massive, he prefers to increase the number of fields and therefore the number of beams, rather than the voltage.

The late Dr. Arthur C. Heublein considered that "in order to take advantage of the varying times of mitoses in the tumor cells, total irradiation should be of low intensity so that it might be given continuously over a comparatively long time and that it should be as nearly homogenous as possible in its distribution throughout the body." The first report of results of the Heublein method of therapy was published in 1934. At the time of institution of this technic, "the hope was entertained that general irradiation in small doses might stimulate in some manner a defense mechanism in man against the growth of cancer" (108).

Medinger and Craver (372) report the treatment of 94 cases of Hodgkin's disease by the Heublein method. These authors use 185 kv., 1 ma., a 5.5 mm. copper equivalent filter and a 3 meter distance between the roentgen tube and the patient. The output of their machine is about 0.86 r per hour giving about 17 r per day. A dose of 100 r therefore requires 6 days. 300 r is considered the upper limit of safe dosage for a patient in reasonably good health. Before giving total body irradiation, Medinger and Craver advocate 2,000 to 2,400 r of high voltage therapy locally for the early case and 400 to 1,200 r to areas showing maximum involvement in generalized cases. Their best results with this method were seen in cases of early localized disease.

Many radiologists consider this method of therapy unnecessary (380) and others consider it highly dangerous (201, 273). There is little question that a thoroughly trained staff in a well equipped hospital is necessary to use the technic safely and advantageously.

"On the assumption that hyperactivity of the leukopoietic tissues is related to the over-irritation of the leukopoietic centers," Langer (317) treated a series of cases "by roentgen irradiation over the centrum of the vegetative nervous system and its paravertebral ganglia." In addition to the autonomic nervous system irradiation, Langer treated the enlarged masses directly. He believes that the enlarged nodes respond better to direct treatment after paravertebral irradiation has been applied.

2. RADIOACTIVE SUBSTANCES

Roentgen therapy is used much more extensively in the treatment of Hodgkin's disease than is radium, because the direction and degree of penetration of its rays may be regulated and because areas at varying distances beneath the surface of the skin can be treated reasonably effectively. Radium is most useful for the local obliteration of a circumscribed region of tissue immediately surrounding it. The likelihood of skin damage is greater when radium is used. A combination of roentgen radiation and radium has been suggested: "...Soft roentgen rays and alpha and beta radium rays produce necrosis of all exposed tissues and show little or no selective action. They lead to long-continued, imperfect and atypical reparative processes...carcinoma and sarcoma often resulting... High voltage Roentgen rays are less selective on tumor cells and produce more injury of stroma cells and vessels...There may be an advantage in combining Roentgen rays and radium in the treatment of tumors" (148). "I have recently been engaged in a comparative study of the two agents, radium and the Roentgen ray...the reduction of glands whether deep or superficial is much more rapid from radium than from Roentgen rays; furthermore, the effects are obtained with much less general upset to the patients" (59).

The advantage of radium's physicobiologic activity has been reduced by the inaccessability of deep structures and by the impracticability of application over large areas. These objections are overcome to some extent by the use of radioactive materials administered intravenously. Perhaps the best known of these substances is radioactive phosphorus. Although the use of this material in the therapy of Hodgkin's disease has been described previously (156, 232, 339), Hoster, Doan and Schumacher's report (248) is the first solely devoted to the hematologic study and clinical evaluation of its usefulness in Hodgkin's disease. Isotonic disodium phosphate solution with an initial activity

of 200 μc. per cu. mm. was given to 11 patients with Hodgkin's disease, 6 of whom had had no previous therapy. The average biweekly dose was 2.31 mc. and the treatment was given over a period of 10 to 37 weeks. During the course of therapy, depression of hematopoiesis, particularly of the platelet series was noted in a majority of patients, and 10 of the 11 patients showed additional adenopathy or evidence of new bone involvement while the treatment was still in progress. Hoster and associates conclude that radioactive phosphorus is not of therapeutic value in this disease.

The disappointing results following the use of soluble radioactive phosphorus in Hodgkin's disease have been attributed to the failure of suitable selective distribution of the phosphorus in the lymphoreticuloendothelial system following its intravenous and oral administration. The availability of many hitherto untried radioactive materials obtained from the cyclotron and the atomic pile has increased the possibilities of achieving such selective distribution. Recently, colloidal radioactive manganese has been used by Hahn and Sheppard (222). "If, when given by vein, the distribution of highly dispersed sols is in rough proportion to the amount of lymphoid tissue (as has been suggested . . .), one might reasonably expect to obtain a desired selective radiation effect on those tissues which are commonly affected in chronic lymphatic leukemia, Hodgkin's disease, reticuloendotheliosis and in certain cases of lymphomas." Hahn and Sheppard (222) prepared a colloidal solution of radioactive manganese, which has a half-life of 310 days, emits desirable emanations and is an element of known chemical behavior. They injected this substance intravenously into a small number of Hodgkin's patients and noted marked reduction in the size of involved lymph nodes, as well as remission of fever. . ."its use in the radiation therapy of Hodgkin's disease. . .would seem to be indicated."

Blau, Sinason and Baudisch (39) studied the properties of colloidal gamma ferric oxide made radioactive by absorption of radium gas (radon) and suggest that it may be useful in the treatment of reticuloendothelial diseases. Gamma ferric oxide retains its catalytic properties in the colloidal state and is taken up by the reticuloendothelial cells after intravenous administration. There are said to be no toxic effects attending its use. The radioactive substances contained in the colloidal mass have a half-life of about 27 minutes and emit alpha, beta, and gamma rays in desirable quantities and sequence.

The intravenous administration of radium salts is a dangerous procedure (474), but one gratifying result is reported by Stevens (494). A man with Hodgkin's disease was treated by repeated injections of radium salts; 440 μgm. of radium were given over a period of 5¾ years. The patient developed severe radium poisoning but was alive with no signs of Hodgkin's disease 18 years following treatment. The patient did not develop a sarcoma or carcinoma in spite of the large amount administered. "It is possible that the chemical processes which led to the apparent cure of the Hodgkin's disease may have produced in the patient's body cancer-resistant materials and so have counteracted rather than favored any carcinogenic tendencies of the radiation." Severe pains, experienced by the patient because of mandibular necrosis, were treated several times with pronounced relief by a special calcium free diet and ammonium salts.

3. BIOLOGIC EFFECTS OF RADIATION

The complications of radiation may range from slight malaise to death. Gastrointestinal disturbances, weakness, apathy and fever are relatively innocuous consequences of this method of therapy. Leukopenia and purpura are more alarming. Activation of old tuberculous foci may endanger life, as may severe skin burns, pulmonary fibrosis or irradiation pneumonitis. The development of carcinoma and leukemia in Hodgkin's patients has been ascribed in some cases to prolonged and excessive exposure to Roentgen rays.

Radiosensitivity.—The lesions of Hodgkin's disease are usually radiosensitive. Nevertheless, sensitivity to roentgen rays may vary throughout the course of the disease. In the usual case, radiosensitivity is observed in the early stages and radioresistance is noted late in the course of the disease. It has been observed recently that presumably radioresistant lesions may become radiosensitive again if the patient is successfully treated by methods other than roentgen therapy, such as nitrogen mustard therapy or bacterial polysaccharide therapy.

The cause of radioresistance has been attributed to repeated small doses of roentgen rays over a long period of time (192), fibrosis of the lesions, the development of "tumor producing varieties" of the disease (164, 166) or change in the degree of malignancy of the process. Since all these explanations are conjectural, none are satisfactory. Most cases of Hodgkin's disease, as stated above, eventually show radioresistance despite the best and most judicious use of radiation technics. The most resistant cases are often those which are spreading rapidly throughout the body and frequently these lesions are cellular rather than fibrotic. It is fre-

quently possible to correlate the radiosensitivity of a true neoplasm with the histologic picture; the most actively dividing and most primitive tumors often are the most radiosensitive. No such correlation exists in Hodgkin's disease; in fact, the so-called Hodgkin's sarcoma is often radioresistant.

Individuals vary in their sensitivity to radiation, as apparently do lesions in special locations. Craver, Braund and Tyler (103) found lung lesions to be very radiosensitive although control of these lesions by x-ray is often difficult "because of the nature of the tissue bed." Bone lesions usually respond very well to roentgen radiation. Visceral lesions vary in their radioresistance and sensitivity. In the average early case, all lesions are radiosensitive and, with each recurrence, the resistance seems to increase (208).

Goodrich (203) cites the reported increase in radiosensitivity in the presence of certain dyes and pigments. He injected fluorescein solution intravenously or directly into the masses to be irradiated, gave a full course of x-rays and found that previously radioresistant lesions of 2 cancer patients regressed appreciably. Goodrich described a series of 6 cases of Hodgkin's disease only 1 of which received fluorescein in addition to x-ray. This patient was the only one of the 6 who lived more than 3 years. These data are too meager to be of significance. Goodrich reasoned that "fairly soft radiation exerts an increased ionization effect on a scattering medium containing small amounts of fluorescein," and concluded that fluorescein increases the sensitivity to radiation.

Arons and Sokoloff (12) recommend the use of congo red as an adjuvant to the roentgen therapy of neoplasms. They state that in a series of 70 patients the adverse effect of roentgen therapy was reduced by the use of this material. There was a return toward normal of polymorphonuclear leukocytosis, lymphopenia and thrombocytopenia, and a decrease in "roentgen sickness." In addition, congo red is said to have an inhibitory effect upon tumor growth in certain animals. Arons and Sokoloff's work was published in 1939; confirmation of their results has not been reported.

General metabolic effects.—On the theory that they produce cellular and metabolic effects similar to radiation, certain chemicals have been used as an adjuvant to x-ray. Werner (quoted by Ewing [148]) hypothesized that radiation splits lecithin in the cells and produces choline and that choline has a prominent action in inducing the cellular changes following radiation. By injecting choline or a combination of choline and boric acid (enzytol), Werner observed changes in the cells of lymph nodes, spleen, testis and ovary which he regarded as identical with those following irradiation. The intranuclear changes were said to be most striking in this respect. Hydrochloric acid, trypan blue and trypaflavin are said to cause a similar nuclear degeneration in the thymus and germinal centers of lymph nodes and spleen. Following acute arsenical poisoning the lymphoid organs are said by Watjen (148) to contain nuclear changes similar to those seen after irradiation.

The question of the effect of roentgen rays on the patient with Hodgkin's disease is of considerable importance since this method of therapy is not only one of the most effective now available, but its use is attended by remissions which may last for a period of 1 year or more. Whether these remissions are always a direct result of the therapy has not been established definitely since remissions of similar duration have occurred spontaneously in patients with chronic Hodgkin's disease. Medinger and Craver (372) observe, in this connection, that the rate of survival beyond 10 years is almost the same among untreated as among treated cases. The beneficial effects observed in many cases following teleoroentgen therapy has led to the conclusion that the value of this method "depends ... on the improvement of the constitution of the patient" possibly with an increase of the patient's resistance to his disease, through some autonomic nervous system change (192) or by an unknown mechanism (372).

Ewing (148) recognized the constitutional factor involved in the beneficial effects of radiation on tumors. He cites the work of the following investigators in this regard. Holthusen (241) maintains that there is a general non-specific immunization against the tumor following the destruction of protein by roentgen rays. Doerr and Berger (134) find an increase in clotting time and serum globulin after roentgen radiation which they consider the result of the "action of mobilized proteins." Knipping and Kowitz (298) believe that there is the same increase in fibrinogen and globulin and decrease in albumin in the blood after irradiation that is found after the injection of foreign protein. In studies of rats, Handel and Tadenuma (225) observed that the metabolism, decreased by sarcoma, was increased by irradiation, and they conceive that the toxic products discharged from the tumor are at the same time reduced by the irradiation. Caspari (72) and Freund (175) believe that the body is immunized by the proteins derived from the necrosing tumor cells. Mahnert (349) maintains that radiation destroys the glycolytic property of tumor cells and stops the production

of lactic acid; and, for this reason, it is thought to restore the normal carbohydrate balance and conserve the stores of glycogen.

Ewing (148) emphasized the importance of the whole body in the radiation cure of carcinoma and cited the experiments of Kok and Vorlaender and of Caspari (72) in which irradiation of the whole animal was more effective than the same dose applied to the tumor bed alone; at times, under the conditions described, general irradiation caused the regression of animal tumors protected from the direct rays. "Vigorous reactions to irradiation fail in the debilitated subject, therefore the radiologist must use every intelligent medical and hygienic method that may improve that patient's general health." Ewing concludes: Observations are accumulating that show irradiation not only destroys tumor tissue but may exert a favorable influence on the nutrition and metabolism of the body as a whole, reducing the deleterious effects of the tumor and possibly causing some general non-specific protein immunization which increases the resistance of the body against the tumor and, in favorable cases, may even throw the balance of nutrition decisively against an unstably nourished neoplasm."

Effects on normal tissues.—Before considering the specific changes in the lesions of Hodgkin's disease following irradiation, it may be valuable to review the effects of roentgen rays on normal lymphoid tissue. The lymphocytes are probably the most actively growing cells in the body and are very sensitive to irradiation (166, 390). It is impossible, however, to administer a dose of roentgen radiation sufficient to produce involution of all lymphoid tissues without seriously damaging other tissues (255). Extensive destruction of lymphoid tissue can be brought about in lower vertebrates as well as in mammals, suggesting that the radiosensitivity may be a property of the lymphocyte itself. It is interesting, however, that the destruction of lymphoid tissue is largely abolished if the blood supply is cut off by ligature (275). Small doses of roentgen rays cause lymphocytic hyperplasia while large doses are said to depress the number of lymphocytes (166). Very small doses of radiation may produce a transient lymphocytosis while a transient leukocytosis follows both large and small doses. Leukopenia and lymphopenia follow the transient effects after 1 to 3 days and persist for from 2 to 3 weeks (390). Irradiation is followed by a moderate hyperplasia in the cords and follicles. If subjected to repeated exposure, cells resembling the normal lymphoblasts develop. These latter cells are known to be somewhat resistant to the action of roentgen rays (165).

In opposition to these generally accepted hypotheses concerning the radiosensitivity of lymphoid tissue are the conclusions of Ewing (148) and Brunschwig (48) who believe lymphatic tissue to be resistant to the action of roentgen rays. The former author describes the following changes in normal lymph nodes after irradiation:

(a) Transformation of the germinal center into a compact ring of flat cells resembling squamous epithelium.

(b) Replacement of the germinal centers by lymphocytes.

(c) Obliteration of follicles but persistence of lymphocytes.

(d) Reticulum cell hyperplasia.

(e) Recovery or lymphoid hyperplasia after 3 or 4 months.

A common basis for the various effects of roentgen rays, estrogens, androgens, carcinogenic hydrocarbons and adrenal cortical extracts, all of which are said to exert effects on lymphatic tissue, has not been determined. Roentgen rays alone or with carcinogenic hydrocarbons may cause lymphoid neoplasia or leukemia under certain specific conditions. Estrogens definitely increase the incidence of lymphoid neoplasia in mice (186) but "seem to cause atrophy of thymic and possibly other lymphoid tissues in the rat" (454). In dogs, estrogens in large doses damage both myeloid and lymphoid tissues (516). Androgenic sterols are said to decrease the incidence of lymphomatosis in estrogen-treated mice (187). Adrenal cortical extracts deplete the lymph nodes of lymphocytes and inhibit lymphopoiesis in mice (136). The latter hormone exerts mild inhibitory effects on transplanted rat lymphosarcoma and rat leukemia (231). Failure of typical post irradiative lymphoid changes to occur in nodes whose afferent vessels have been ligated may be explained on the basis of a hypothetical humoral factor whose action is prevented by ligation (275). The relationship of the lymphoid system and the organs of internal secretion is currently under study by numerous investigators.

Effects on pathologic tissues.—When nodes which have been involved by Hodgkin's disease are irradiated, the following changes are described:

1. Large foci of necrosis appear (48, 192).

2. Lymphocytes and lymph follicles are among the first to diminish in number and size (48, 166, 192, 442).

3. The reticulum cells show pyknosis, karyorrhexis and necrosis or undergo abnormal reactions with bizarre-shaped mitotic figures and irregular giant cell formation (442).

4. Eosinophils, polymorphonuclear leukocytes

and Sternberg-Reed cells become fewer in number and may disappear entirely (48, 166, 192).

5. There is more phagocytosis by "large cells with vesicular nuclei" (166), and mitoses become very rare (192).

6. The fibrosis which follows the cytolytic action of the rays is diffuse but dense, and hyalinization may occur (48, 166, 192, 311, 442).

7. After a latent period the cellular tissue which was diminished by radiation begins to proliferate and infiltrate the surrounding sclerotic areas. This constitutes a recurrence and is attended by round-cell invasion and increased numbers of eosinophils and reticulum cells (48).

8. Complete sclerosis constitutes a "local cure" (48, 192).

Fox and Farley (166) consider the reaction to roentgen radiation to resemble the "coarse and deforming fibrosis to be seen in late stages of tumor-forming Hodgkin's disease, and might be described as an accelerated natural course of events." Rosenthal (442) observes that cytolytic modifications similar to those produced by roentgen radiation are also seen in untreated nodes.

Effects on blood.—In patients with Hodgkin's disease receiving roentgen radiation to localized sites of the disease there is said to be a transient leukocytosis (311, 390) followed by a fall in lymphocytes (200, 311, 390). Although most investigators state that the polymorphonuclear elements usually decrease, Fox (165) reports that in Hodgkin's disease these cells are "indifferent to irradiation except in malignant and febrile cases." Eosinophilia and thrombocytosis when present are increased following roentgen therapy (311), if the dose is not large (243).

The blood response of patients receiving total body irradiation for Hodgkin's disease is similar to that seen following local application. There is a transient increase in the red and while blood cell series lasting from a few hours to days. The maximum changes are seen at the end of 2 to 3 weeks and may persist for months (390). In 50% of a series of 94 patients there was a decrease in circulating white blood cells, in 23% to neutropenic levels. In the experience of Medinger and Craver the changes in hematologic equilibrium depended on the general condition of the patient, the activity of the disease, the cellular levels at the onset of treatment, the amount of previous roentgen radiation and the dose of roentgen radiation being given. These authors noted, not infrequently, that in patients who began therapy with a leukopenia as a result of the disease there was an increase in the cell count after therapy.

In a group of 450 cases including all types of "lymphoblastoma" (Hodgkin's disease, lymphatic leukemia and lymphosarcoma), Decker, Leddy and Desjardins (124) found the following blood changes:

(a) In a group with normal initial white blood cell counts, the loss after 1 week was 22.4% and after 4 weeks 33%.

(b) In patients presenting initial leukocytosis, the loss after 1 week was 58.8% and after 4 weeks 50.9%.

(c) In patients with initial leukopenia, the loss after 1 week was 16% and after 4 weeks 10%.

(d) When there was initial leukocytosis, the decrease in total white blood cells was due to destruction of polymorphonuclear leukocytes rather than lymphocytes, "the explanation of which is obscure and deserves study."

The blood changes in cancer patients following roentgen radiation are similar to those in patients with Hodgkin's disease who have been irradiated (390).

The ultimate chemical reactions responsible for the constitutional and local effects of roentgen rays are not yet understood. Recently, Abels and associates (1) undertook an investigation of the relationship between the metabolic effects of radiation and phosphorus metabolism. They found that the administration of subtherapeutic amounts of radioactive phosphorus to 5 patients with leukemia was followed by an alteration in the organic acid-soluble fraction of the phosphorus in the erythrocytes and leukocytes. The administration of non-radioactive phosphorus was not followed by a significant rise in this fraction of the blood cells. These same alterations were observed after administration of very small doses of total body roentgen radiation to 3 patients and after irradiation of the blood through a precordial port in 3 patients. "The organic acid-soluble phosphorus compounds are connected intimately with the cellular enzymes which control respiration and carbohydrate metabolism. Such a disturbance may prove detrimental to the normal functioning of a cell. It is possible, therefore, that when therapeutic amounts of radiation are administered, these enzyme systems are so profoundly disturbed that no recovery to the normal state is possible, and as a result, the cell is permanently damaged or killed. Alteration in phosphorus metabolism appears at present to be the most sensitive index of exposure to irradiation." These experiments were performed

only in patients with leukemia and normal controls were not used.

4. SURGERY

The usefulness of surgery in the therapy of Hodgkin's disease has been a controversial issue for many years. At the present time, almost every patient is subjected to a surgical procedure in order to secure a biopsy specimen. Many surgeons recommend that patients with localized disease receive the benefit of radical excision at the home of biopsy (18, 91, 166, 181, 268, 389).

In many cases, surgery is said to give better results than x-ray alone if the patient is treated sufficiently early. If combined with prompt postoperative irradiation in doses kept within the safe limits of skin tolerance, surgery in localized Hodgkin's disease, involving groups of accessible nodes, is said to give much better results than are usually expected (268, 455, 477). The surgical risk in these cases is rarely greater than that involved in the use of roentgen radiation designed to eradicate the localized lesions.

Yates (565) argues that effective treatment must remove the disease, if possible, and conserve the defensive powers of the body. Complete removal of involved lymph nodes, wherever they are accessible, not only achieves the former but helps with the latter since "an abundance of lymphocytes about the local lesions and in the blood stream indicates a more complete defense" and excision induces "compensatory lymphoid hyperplasia." Moreover, "the local recurrences after surgery have a tendency to exhibit an increasing chronicity as judged by the histologic picture. One case with a recurrence after 4 years showed only adenitis." Following operation Yates advocates subjection of the entire area to roentgen radiation followed by exposure to the sun "which induces desirable lymphoblastic stimulation." Yates became very skilled in the technic of lymph node excision and had few untoward reactions following widespread removal of nodes. Willis (Guerriero [220]) relates that Yates treated the former's son for Hodgkin's disease by widespread removal of nodes all over the body followed by anti-diphtheroid horse serum in large quantities. The patient has never had a recurrence and at the time of the report, 16 years later, was perfectly well.

Some of the results obtained after radical surgery are recorded as follows:

(a) 10 and 12 year freedom from disease, alive and well (18).

(b) 8 and 11 year freedom from disease, alive and well (477).

(c) 7 and 16 year freedom from disease, alive and well and 34 year survival, at present free of disease (268).

(d) 5 year freedom from disease, death due to Hodgkin's disease (477).

(e) 24 year freedom from disease, death due to Hodgkin's disease 3 years later (268).

It is important in evaluating these results to remember that only selected cases with localized disease receive the benefit of radical surgery. Nor can any of the above cases be considered cures since recurrences after very long periods of freedom from disease are described in some cases not subjected to radical surgery (477). In some cases with prolonged survival, restudy of the histopathologic features of the biopsy specimen has failed to confirm the original diagnosis of Hodgkin's disease (96). This type of error in diagnosis may be more common than is generally believed.

Gastrointestinal surgery for Hodgkin's disease involving this area carries with it a considerable risk. Such a procedure is indicated, however, if the lesion is primary and localized. Survival from the immediate effects of the surgery confers as much as twice the usual life expectancy on the patient thus treated (106, 477).

Some authorities consider surgery to be useless (81, 120, 164, 192) maintaining that severe toxemia may follow surgery with rapid progression of the disease. Burger and Lehman (58) achieved no better results with surgery alone than with the use of irradiation alone. Many individuals, however, believe that the removal of an important focus of the disease causes temporary recession of the remaining lesions (538). Moreover, modern surgical technics have eliminated many of the so-called "toxic post-operative reactions." The minimal trauma and nonspecific inflammation associated with incision, manipulation and repair, however, has not been eliminated and in some cases appears to increase the rate of progress and extent of dissemination of the disease.

Surgical intervention in the course of Hodgkin's disease may be necessary to relieve distressing and dangerous pressure symptoms. In paraplegia, prompt removal of the spinal cord block is said to be indicated in order to prevent permanent damage. Since epidural infiltration is often decidely fibrous, laminectomy may be required before deep x-ray therapy will be effective in the treatment of the spinal cord compression (213). However, complete relief from the symptoms of myelitis has been obtained many times by means of roentgen therapy alone.

5. GENERAL SUPPORTIVE TREATMENT

The patient with Hodgkin's disease should be given continuous and adequate general supportive therapy. Of great importance is the maintenance of morale and the correction of a depressed mental state if it is present (268). A high-calorie and high-vitamin diet, heliotherapy, fresh air, rest, relaxation, removal of known foci of infection and avoidance of upper respiratory infections will unquestionably increase the well-being and probably prolong the life of the patient. Exposure to the sun or to ultra-violet light may help to combat lymphopenia (230), and it is the experience of many patients that they feel better if they are out of doors taking a limited amount of physical exercise (260). It has been observed that patients who live in the country seem to tolerate their disease better than those in urban centers (192). This observation, however, remains controversial.

The advisability of specific vitamin therapy is still in doubt. Large vitamin C deficits have been noted in patients with Hodgkin's disease (530). Spray roentgen radiation plus massive doses of viosterol have been used in the case of a patient with severe pruritis with good results (268). A study of advanced cases with epigastric pain as a persistent symptom has revealed this symptom to be due to erosion of the gastric mucosa on the basis of avitaminosis; therapeutic and postmortem studies are said to support this hypothesis (201). Advanced vitamin A deficiency has been observed in one patient (197); it is not unusual, however, to find extensive involvement of the liver in any disease process associated with A, B and K vitamin deficiencies. It is interesting moreover that following irradiation lymphoid tissue shows morphologic changes which are thought to resemble those seen following prolonged vitamin B deprivation.

Studies concerned with the vitamin metabolism of patients with Hodgkin's disease have, in general, been incomplete. Until more investigation is carried out, supplementary vitamin administration may be recommended with safety as part of the general supportive treatment and should be increased whenever warranted by clinical developments suggestive of specific deficiencies.

Therapy which is helpful in combating anemia is said to be indicated during the early stages of the disease as prophylaxis and later to increase the production of hemoglobin (201). Although adequate protein intake and supplementary iron are helpful, frequently transfusions must be given to bring about the desired effect. "Blood transfusions should be given before the red count falls to low levels. . .we believe that a red cell count of 4 million cells calls for a transfusion unless, of course, the anemia is due to some other cause which is amenable to therapy" (260). Davis (123) has published a report recommending the use of folic acid in association with roentgen radiation and in bone marrow exhaustion due to the disease itself. Although the general measures which have been discussed are simple and usually beneficial to the patient, they are frequently neglected (260).

6. VACCINE AND SERUM THERAPY

Vaccines.—There have been repeated attempts to treat Hodgkin's disease by means of tissue extracts, "immune" sera and other "biologicals." In general these have given disappointing results. Efforts to create or prepare a potent therapeutic material continue. Because active work is being done at the present time in this field and because previous attempts have given such erratic results, the subject is reviewed in detail.

Soon after an attempt was made to implicate the diphtheroid organism as an etiologic agent in Hodgkin's disease, vaccines of this organism were investigated. Billings and Rosenow (37) prepared autogenous vaccines from heat-killed organisms and treated 12 patients. Roentgen radiation was used concomitantly in 9 cases. The results ranged from death following one injection to clinical arrest for the 6 month period that the patients had been under observation. Mellon (377) prepared cultures of organisms found in excised nodes which he used as vaccines. No favorable results were noted. Fox (161) used autogenous diphtheroid vaccine in 2 cases; 1 showed improvement with roentgen radiation and vaccine; he had been improving previously with roentgen radiation alone. The other patient died shortly after institution of treatment. Yates and Bunting (567), two of the original champions of the diphtheroid etiology of Hodgkin's disease, advocated the use of a vaccine of these organisms as an adjuvant to other therapy but admitted "vaccine alone has not worked in our hands." One case, cited in a report by Guerriero (220), was treated by Yates with extensive surgical removal of involved nodes followed by large quantities of antidiphtheroid horse serum; the patient was reported to be in good health without recurrence for 16 years.

Gordon and associates (204, 206-208) reported "elementary bodies" in the extracts of nodes of Hodgkin's disease in large numbers and in what was described as "pure culture." In appearance and staining reaction, they were said to resemble the Paschen bodies of vaccinia but were slightly larger. Gordon reasoned that, if the elementary bodies which he found were the cause of the dis-

ease, resistance might be stimulated in early cases by small doses of causative agent. He tested 18 specimens of serum with various antigens prepared from nodes to determine whether flocculation of the bodies occurred and recorded irregular results. A vaccine of the elementary bodies prepared from the patient's own nodes and "attenuated" by heating to 56° C. for 30 minutes produced reactions in a small number of patients even in small doses. Gordon "sensitized" the vaccine with an antiserum produced in the rabbit; but, despite this later modification, reactions were encountered. "Either the antiserum was not sufficiently potent or the dose of vaccine was too large." The method of preparing the sensitized vaccine is as follows: A rabbit is given 5 to 6 injections of vaccine in increasing doses and when a flocculation-producing antibody against the vaccine is present in demonstrable quantity, the serum is collected. The serum and vaccine are incubated in a tube, the flocculate is permitted to settle, the supernatant is discarded following centrifugation and the flocculate is suspended in phenol saline (0.5% phenol), centrifuged and resuspended several times. In this manner the "sensitized" bodies are washed. The final suspension of vaccine is stored in phenol saline.

The dose of vaccine was adjusted according to the "age, chronicity, temperature, reactions in the nodes and weight change of the patient." The most dangerous complication during the treatment was infection. The reaction to injections of the sensitized vaccine included a temporary rise in temperature, "a sense of tightness, tingling and tenderness" in the nodes, pruritis of the skin over the nodes, and temporary exaggeration of existing pruritis all over the body.

Warner (541) used the sensitized vaccine in a series of 7 cases with the following results:

1. A case which could no longer tolerate roentgen radiation and which was rapidly failing gained weight on vaccine therapy; the nodes became half their former size and no new ones appeared. Signs of myelitis previously present disappeared. The patient developed an initial and later a recurrent hemolytic streptoccic infection and died. At autopsy, miliary tuberculosis was found to be the cause of death and all of the patient's nodes were very small.

2. In a female with early Hodgkin's disease (no biopsy and nodes only in the chest) there was regression and disappearance of mediastinal nodes under vaccine therapy. The general health was excellent.

3. A male with generalized Hodgkin's disease was given very small doses of vaccine and though his condition remained poor at the time of the report, he had "improved a great deal."

4. A 14 year old boy was observed in the hospital for 2½ months while his vaccine was being prepared. During this time, his spleen was palpable, he had a consistently elevated temperature, lost weight and became progressively more anemic. On vaccine therapy he gained weight, the anemia decreased and the spleen could no longer be felt; the lymph nodes neither increased nor decreased in size. The patient was then given 2 doses of roentgen radiation and the nodes almost disappeared. The patient appeared in perfect health; for 2 years no vaccine was given and following this there was a recurrence. The patient was being given an additional course of vaccine therapy at the time of Warner's report.

5, 6, and 7. In these 3 cases vaccine failed entirely.

In another publication, Warner (542) reports 4 more cases. These patients were given no treatment other than sensitized vaccine; they were watched for a period of 3 years; all 4 responded to the treatment. Warner concludes that the sensitized vaccine is an active therapeutic agent.

Since 1937, no reports on Hodgkin's disease have come from the laboratory of Gordon and his coworkers. The experiments with elementary bodies are of considerable interest but one feature stands out particularly. Gordon refers repeatedly to the reactions produced by the unsensitized vaccine. These very reactions led him to attempt "sensitization" of the vaccine. It is easy to understand why the sensitized vaccine should produce reactions since it contains foreign protein of the rabbit; this, however, is not true of the unsensitized material.

Wallhauser and Whitehead (537) used an autogenous glandular extract, reasoning that small amounts of the toxins of Hodgkin's disease are present in the involved node. They further hypothesized that the production of antibodies might be stimulated by sub-cutaneous injection of small amounts of the node extract. The extract is made by maceration of the nodes, preferably the soft cellular variety, followed by filtration through a Seitz filter; the filtrate is injected subcutaneously. Individual tolerance varied considerably and Wallhauser and Whitehead noted that cachexia increased if the dose was too large. The patients who received the vaccine were given no other treatment. The results included softening of enlarged nodes and eventually regression to a very small size and disappearance; a reduction and disappearance of the cachexia associated with the disease

and relief of symptoms such as nausea, vomiting, urinary retention and asthenia; and a fall in temperature and gain in weight.

Wallhauser and Whitehead conclude that "certain cases of Hodgkin's disease may be treated with an autogenous glandular extract, with the hope of good clinical results without the use of x-ray." They caution the therapist to avoid bacterial contamination, to use fresh extracts and to give injections regularly over a long period of time, with occasional rest periods.

In addition to these experiments by Wallhauser and Whitehead, there are sporadic reports of the use of vaccines made from Hodgkin's nodes. Utz and Keatinge (519) used node filtrates in 9 patients, 5 of whom died within a year. A vaccine was made from the node of one case and given to another without beneficial effects (457). In one case, Fraser and Mekie used autogenous Hodgkin's extract (the filtrate of emulsified nodes) without improvement (171). Schreiner (456) reports that in one case a node was removed, autolyzed and the filtrate reinjected with no observable results. Cunningham (113) used vaccines on several of his series of 25 patients without success. Hanrahan (226) treated 9 patients with an autogenous node filtrate; 5 (3 of whom had very transitory remissions) died. None of the others improved appreciably. All were moderately advanced cases.

Serums.—Gow (208) gave a goat repeated injections of Hodgkin's lymph node emulsions. One patient with advanced disease was given several inoculations of goat serum with no obvious effect.

Utz and Keatinge (519) used chicken anti-Hodgkin's tissue antiserum reasoning that Hodgkin's disease is due to the avian tubercle bacillus. Nodes of the soft cellular variety were removed, part was saved for histopathologic study and part injected into a hen subcutaneously. Ten days later the hen was bled, the serum removed and gradually increasing doses were injected into the patient at prescribed intervals. Severe reactions often followed. Usually the more severe the reaction, the better the later response. "If the response is slow, a single dose of x-ray is sufficient to produce a normal condition." No controls of normal hen serum were used. "Preliminary results were encouraging."

McGrath (368) attacked the work of Utz and Keatinge in the following statement: "The method . . .is based on the hypothesis that Hodgkin's disease is due to infection by avian tubercle bacilli. There are many reasons to doubt this hypothesis. Moreover, if it were correct, treatment by an immune serum would not, on the analogy with other tuberculous disorders, be likely to be of value. There are, however, many examples of successful therapy based on fallacious theories, and the claims of the authors encouraged a trial." The only modification of treatment was phenolization of the serum following its filtration through a Seitz filter to prevent infection. McGrath treated 4 cases without favorable results. Pulvertaft (425) used the serum for 4 cases with subjective improvement in all, but with quick return of symptoms and lymph node enlargements despite continued therapy. Barrett and Bond (22) found the reactions to chicken serum troublesome and occasionally dangerous. One of their patients had severe anaphylactic symptoms several times; trial in 4 cases was attended by no noticeable response in 3. In one patient there was pronounced improvement, but within a short period he experienced a relapse and died.

In the therapy of Hodgkin's disease complicated by brucellosis, Wise and Poston (558) report "Immune serum therapy, utilizing whole blood or blood serum from persons recovered from brucellosis or having agglutinins in high titer has been combined with the use of sulfapyridine, but the effectiveness of these sera has not been demonstrated. Since recent investigations in this laboratory have shown that Brucella organisms isolated from many of the patients suffering from Hodgkin's disease, possessed capsules and show significant antigenic differences from the laboratory strains, further consideration must be given to the antibody properties of the serums used in the treatment of Brucella infections."

Recently, the antireticulo-cytotoxic serum of Bogomoletz (ACS) has been used in the therapy of Hodgkin's disease. This material would logically be expected to affect the reticuloendothelial system since it is an anti-human bone marrow and spleen antibody developed in an experimental animal. Most of the Hodgkin's patients who have received ACS had far advanced diseases. In general, the results have been poor although a few evanescent signs of improvement were noted. It is very difficult to evaluate the effects of the serum since no prolonged beneficial results were obtained.

Hoster and his associates (243) treated a group of patients most of whom were in advanced stages of the disease. Improvements noted did not last long enough to make them of therapeutic significance. Malisoff (351) states that the use of ACS in 21 cases of Hodgkin's disease resulted in temporary improvement in 70% of the cases as shown by 25 to 75% shrinkage in the size of involved lymph nodes and by loss of other unfavorable symptoms. Reduction of pain is said to be very

marked. Prolonged use in early cases has not been given adequate trial (243, 351).

Hoster has suggested that the antibodies developed by Gordon, Wallhauser, Gow, Utz and Keatinge, McGrath, Pulvertaft, and Barrett and Bond following the injection of extracts and emulsions of Hodgkin's tissue into experimental animals may be similar to those present in ACS and that temporary favorable results noted by some of these workers may have been attributable to the presence of anti-human antibody in the material injected.

7. CHEMOTHERAPY

The specific therapeusis of Hodgkin's disease by chemotherapeutic agents has not been accomplished. The list of compounds which have been administered to patients with Hodgkin's disease orally, locally or by injection includes almost every pharmacologic category:

> quinine, iodine, phosphorus, benzene (519), methenamine, biotin, emetine hydrochloride, emetine, bismuth, iron, cod liver oil, sodium salicylate (268), diaphorase, gamma butyric acid, folic acid, meostam, choline chloride, colchicine, urethane, belladonna and glycerine (368), mercuric inunction (396), phenol and olive oil (268), diuretics (201), calcium gluconate, acetyl salicylic acid (81), antimony (81), corrosive sublimate, chaulmoogra oil and esters (429), trypan blue, colloidal manganese, colloidal gold, sanocrysine, mercury, potassium iodide, belladonna, glycerine, pyrifer, creosote, silver nitrate, chromic acid, carbolic acid, sulfanilimide, sulfapyradine (33), penicillin, streptomycin and arsenic of all varieties (81, 396): Fowler's solution, arsenous oxide, colloidal arsenic trisulfide, sodium acetyl arsanilate, arsphenamine, neo-arsphenamine, sodium cacodylate, sodium arsanilate and arsazetin (360).

The drugs most commonly used in the therapy of Hodgkin's disease are the following: iron, arsenic, cod liver oil and vitamins. The so-called "tonics" are advocated (120, 273, 343, 396, 438, 564) because they can do no harm and often are said to increase the well-being of the patient. The statement that arsenic has a specific action against the disease has been questioned; one patient developed Hodgkin's disease while receiving arsenic therapy for syphilis. The mechanism by which arsenic operates in Hodgkin's disease is not understood. It is interesting that, following acute arsenical poisoning, the lymphoid organs are said to exhibit some of the nuclear changes observed after irradiation (148). Enthusiasm for arsenic has decreased during recent years; few recent workers consider it useful.

Although the sulfonamides have not had an extensive trial, results have been essentially negative to date. One series of 18 febrile patients received sulfonamide chemotherapy without appreciable decrease in temperature (201). A patient with cutaneous Hodgkin's disease was given a course of sulfapyridine without beneficial effect (558). Streptomycin apparently has no greater usefulness than the sulfonamides although the number of patients treated has been small. Penicillin, in doses of 3 million units per day, given over a period of weeks, has been used in several patients without beneficial effect (445). A series of 3 cases was treated with promin (a sulfone) for a period of several months without noticeable beneficial results (243).

Avidin obtained from egg white has been administered in large quantities to patients with Hodgkin's disease and other neoplasms. The rationale of this therapy is based on the statement that biotin, a member of the vitamin B complex group, is an important factor in neoplastic cellular growth and is considered to have procarcinogenic potentialities (223). Biotin is present in large quantity in vaccinia virus and is found in 3 times greater concentration in tumors than in normal adult tissue. The concentration present in tumors is approximately equal to that in embryonal tissues. Avidin is said to exert a neutralizing or inactivating influence on biotin (281, 435). According to Laurence (319), there are 300 authentic cases of spontaneous recession of malignancy in the literature and 100 of them were associated with acute infection. He reasons that the infection induced a biotin deficiency which in turn interfered with tumor growth. With this hypothesis in mind, 10 patients with diverse malignant processes, including carcinomas, sarcomas, leukemias and Hodgkin's disease, were treated with avidin for one year (281); 7 of these 10 patients also received roentgen therapy. The general condition of all the patients improved. In none of the patients was there a pronounced response; there was said to be a synergism between the action of avidin and roentgen therapy. In spite of large doses of avidin, no symptoms of biotin deficiency developed in these patients. No toxicity attributable to the therapy resulted, and the only metabolic change noted was an increase in non-protein nitrogen of the blood in one patient (230) and a rise of blood cholesterol in two patients (230, 281).

Very recently, Singher, Abels, Craver and Rhoads (476) gave heptylaldehyde bisulfite intravenously to 2 patients with lymphosarcoma and one patient with Hodgkin's disease. The respira-

tory activity *in vivo* of cells from patients with these diseases is said to be depressed by as much as 50% by heptylaldehyde bisulfite. Toxic reactions in the patients treated included diarrhea, headache and small convulsive movements. No effect on the course of the lymphomas was noted. The failure of this drug to act favorably *in vivo* was attributed by the authors to the rapid destruction of the heptylaldehyde bisulfite in the body. "...Compounds must be sought which do not dissociate rapidly. Concentrations of these compounds might be maintained at levels that would destroy the neoplastic lymphomatous tissues" (476).

Nitrogen mustards.—The most stimulating and promising current work in the chemotherapy of Hodgkin's disease is the use of B-chloroethyl amines and sulfides. These sulfur and nitrogen mustards are not only vesicants but also exert cytotoxic effects on a variety of tissues. The susceptibility of cells to their action appears to be related to the rate of cell proliferation. Mitotic arrest during the resting phase of the cycle is seen even after doses well below the toxic level; and extensive nuclear fragmentation is a consequence of somewhat higher doses. Infectivity of the tobacco mosaic and bushy stunt viruses is lost after exposure to the mustard compounds. These effects probably depend on reactions with important biological constituents of the cell. The ability of the mustard compounds to interfere with enzyme systems in general has led to the "enzyme-inactivation" theory of their action in cells. It has also been shown that solutions of casein exposed to mustard gas become ineffective in supporting growth though they are not harmful when fed to animals. Apparently the mustard compounds cause intramolecular changes in proteins; and their residues, attached to amino acids like histidine, lysine and methionine, are not capable of being split off in the body (293, 294). The glucose tolerance is increased (141) and an inhibition in the intestinal absorption of glucose as well as alterations in carbohydrate metabolism have been described (193).

The cytotoxic action of the mustards is first reflected in experimental animals in the lymphoid system and the gastrointestinal mucosa (193, 211). Lymphopenia, granulocytopenia, thrombocytopenia and moderate anemia reflect a depression of all the cellular elements of the marrow. Nausea, vomiting and diarrhea with hematemesis and melena are the early results of administration of large amounts of the drug. Lethal doses cause kidney damage, circulatory collapse, shock and respiratory failure. The outstanding pathologic lesions are found in the intestinal tract, bone marrow and lymphatic tissue with atrophy of the latter (211). The marked effect on lymphoid tissues suggested the use of mustard compounds for the treatment of lymphoma. Sulfur mustards are not suitable for oral administration; the nitrogen mustard [methyl bis (beta-chloroethyl) amine hydrochloride], a water-soluble hydrochloride, is easily administered by vein. Two compounds have been used clinically: tris (B-chloroethyl) amine hydrochloride and methyl bis (B-chloroethyl) amine hydrochloride; the latter has had the more extensive clinical trial (434). The material is given intravenously, rapidly and with care to avoid extravasation and resulting tissue destruction. The drugs are usually administered in doses of 0.1 mgm. per kgm. of body weight daily for 3 to 6 days, this procedure constituting one "course." It should be mentioned that patients with lymphosarcoma, chronic myelocytic leukemia, acute myeloblastic leukemia, chronic and subacute lymphoid leukemia, giant follicle lymphoma, miscellaneous types of carcinoma, multiple myeloma and polycythemia vera have been treated with the nitrogen mustard compounds with variable and less encouraging results. Only the results obtained in patients with Hodgkin's disease will be considered in this discussion.

The first description of a series of cases included 54 cases of Hodgkin's disease; almost every patient obtained some degree of benefit although many were in the advanced or terminal stages of their illness (202, 271). In some cases improvement was pronounced. Remissions up to 18 months have been noted. Early, slowly progressive disease may be attended by remissions lasting from 4 to 8 months or longer following therapy; in less favorable cases, the improvement lasts from 2 weeks to a few months and is usually followed by rapid recurrence of symptoms. The therapy may be repeated as often as the blood count will permit, and although remissions are often progressively shorter in duration, a state of remission has been maintained in one patient over a period of 33 months following the administration of 14 courses of nitrogen mustard. Therapeutic effects of the drug include lowering of elevated temperatures, general symptomatic relief, regression in the size of lymph nodes, liver and spleen and improvement in the general condition. Patients classified as radioresistant may respond favorably to nitrogen mustards; a few patients previously resistant have developed radiosensitivity after a course of mustard therapy (202). The mustard compounds are especially useful when the disease is so widespread that it is impossible to treat it effectively with roentgen therapy. Certain cases of Hodgkin's disease show negligible response to the drug; most of these patients are said to be

radio-resistant as well. Large masses, invasive lesions, and foci in the skin and bone are said to be refractory to the mustard therapy.

The toxic effects of the drug may be divided into those seen immediately and those which are delayed. Varying degrees of anorexia, nausea, vomiting and diarrhea are experienced within 1 to 8 hours after administration of the drug. If infiltration into the subcutaneous tissue occurs during the injection, a severe necrotizing inflammation results locally. A local thrombophlebitis may occur following exposure of the vessel wall to a high concentration of the material (282). Most of the delayed toxic effects (201, 202, 270, 283, 284, 434, 483) are due to damage of the lymphatic tissues and blood-forming organs: A normocytic anemia with a decrease in hemoglobin of not more than 1 gram may occur during the first 2 weeks, followed by a gradual return of the red cell count to normal after 6 weeks; lymphopenia may be profound and may last for 2 to 3 weeks; there may be a period of moderate or severe neutropenia; thrombocytopenia and rarely petechial hemorrhages may appear during the third week. In rare cases neutropenia and thrombocytopenia are profound, requiring penicillin to combat infection due to the former and multiple small transfusions to combat blood loss due to the latter. Hematemesis and melena may occur during this same period in association with thrombopenia and neutropenia (570).

The action and usefulness of mustard compounds appear to be similar in many ways to roentgen therapy. They may be of great value when roentgen therapy is no longer effective, when there is a severe systemic intoxication and when there is generalized lymphadenopathy (271). Mustard therapy is said to have less dangerous toxic effects and to be less expensive than roentgen radiation.

Bone marrow studies reveal a marked hypoplasia to absolute aplasia of all normal cellular elements with replacement by fibrous tissue. After 3 weeks a gradual regeneration of marrow is seen. At first there is a moderate left shift in the erythroid and myeloid elements and a peripheral reticulocytosis (570). Many observers report a relatively complete regeneration of the marrow following therapy; the degree of regeneration is said to be dependent on the condition of the hematopoietic tissue before therapy in some cases.

Small maculo-papular hemorrhagic and pruritic skin lesions were described following treatment in 54% of cases in one series (570). The changes observed in 3 cases studied by biopsy were consistent with a toxic effect possibly due to nitrogen mustard therapy.

Miscellaneous therapeutic agents.—Coley's fluid, which is a mixture of the streptococci of erysipelas and of prodigiosus organisms and their toxins, has been used in the therapy of Hodgkin's disease, lymphosarcoma and other neoplasms (91). The rationale for the use of these toxins lies in the clinical observation that occasionally, following a severe attack of erysipelas, a remission may occur. Miller (382) claims a recovery in one patient following an attack of severe gangrenous herpes zoster and another was well for 10 years after an attack of erysipelas. On the other hand, progression and death following streptococcic infections are not infrequent. The results following the use of Coley's fluid in Hodgkin's disease are poor. Of 14 cases thus treated, there was only one 5 year survival. However, failure to obtain consistently good results has been ascribed to the use of products of variable potency (399). Coley himself had limited faith in the usefulness of his fluid in Hodgkin's disease and suggested that surgery followed by the toxins offered the best hope of cure (91).

Shear and associates (463a) in a series of papers dealing with previous and current investigations described the effect of a bacterial polysaccharide, obtained from *Serratia marcescens* cultures by chemical fractionation, on tumor-bearing animals and selected human subjects. Among the human tumors studied were a small number of cases of Hodgkin's disease.

The results described were somewhat similar in one respect to those obtained by previous workers using other bacterial toxins such as Coley's fluid. It was found that incomplete destruction of tumors occurred when sublethel doses (adjusted to allow survival of most of the animals treated) were used.

The appearance of tumor hemorrhage and necrosis following intravenous or intraperitoneal inoculation of polysaccharide appeared to be in direct proportion to the amount given. The material was said to retain its original tumor destructive property after tryptic digestion. Electrophoretically it was found to contain only one component.

Experimental animal and human tumors were biopsied before and after therapy and interesting nuclear changes were described. In order of occurrence, the following changes appeared: cessation of cell division, increase in the size of the nucleus with blebs on the nuclear membrane, collapse and shrinkage of the nucleus and disintegration of affected cells with only nuclear debris remaining. It was noted that resting cells were capable of remaining intact and that the inhibitory effect of a single dose was limited to a relatively short period of time (48 hours in experimental animals).

The results of therapy in human beings were characterized by the following observations. A single intravenous injection of more than 0.02 mgm. of polysaccharide resulted in an initial chill followed by an average rise in temperature to 105° F. within one hour reaching a peak at the end of 2 hours. After 5 hours the temperature fell to 99 to 100° F. A rise in blood pressure of short duration was followed by a profound decrease in pressure often to shock levels. The blood pressure was observed to return to normal 24 to 36 hours after cessation of therapy. Neither adrenal cortex extract nor blood plasma were found effective in combatting the shock-like symptoms observed. Adrenalin produced only a temporary increase in blood pressure, elevation of the extremities a more sustained improvement. During periods of severe blood pressure depression, anuria occurred.

Headache, lumbar pain and pain at the site of the tumor were troublesome symptoms during the first hour following therapy administration in a number of cases. In one case the temperature about the tumor area was observed to be higher than elsewhere in the body and occasional edema and cyanotic discoloration of the tumor was observed following treatment.

The average decrease in circulating red blood cells after therapy was 0.5 to 1.0 million with a return to normal at the end of 3 to 4 weeks. White blood cell levels from 8,000 to 23,000 were observed on the day following therapy; the principal increase in cells occurred in the neutrophil elements. The range of total dose was 0.03 to 2.0 mgms., the largest number of inoculations given was 14 and the shortest interval between inoculations was 6 hours. Although no tumors were completely eradicated in human subjects, the size and consistency of the neoplastic growths investigated were favorably affected. Roentgen ray resistance was observed to be replaced by sensitivity in one case of Hodgkin's disease treated. Carcinoma was not included among the neoplastic diseases treated, possibly because of the less favorable experimental evidence concerning its effectiveness in animal carcinoma and because human tumors treated with more crude bacterial preparations by other workers have not been greatly benefited. It was postulated that the tumor-necrotizing effect of the polysaccharide may be separate and distinct from the pyrogenic effect.

Normal animal spleen and marrow extracts were given to a few patients by Murray (396) without effect. Two cases (1 treated by roentgen rays and 1 untreated) were given an aqueous splenic extract by Watson (545) with considerable improvement.

Specific internal secretions have been suggested in the treatment of Hodgkin's disease. Gemmell (190) believes that ovarian extract might be given to females with Hodgkin's disease since susceptibility of that sex to the disease seems to be associated with periods of decreased ovarian activity. Insulin was given to one patient in small amounts after he developed glycosuria. Administration was coincident with a clinical remission, withdrawal with a recurrence (425). Adrenal cortical hormone has been used in recent years to combat asthenia, debility and some of the cutaneous complications. There are no definitive results available since this drug is usually used in combination with various other types of supportive therapy.

Malarial therapy has been used for cutaneous lymphoblastoma. By itself, its use is disappointing, "but when followed by x-ray the response is striking" (396). Artificial fever therapy (106° F.) induced in a heated cabinet has been used in the case of 3 patients with advanced disease without benefit (243).

F. The Nature and Etiology of Hodgkin's Disease

As the syndrome of Hodgkin's disease gradually became recognized as a distinct entity during the past century, questions arose concerning its relation to other diseases involving lymphatic tissue. Information concerning these questions has been sought in an effort to establish the disease category in which Hodgkin's disease should be placed. In general, hypotheses fall into one of the following major groups:

1. *Hodgkin's disease is a neoplasm*
   - (a) Of myeloid origin.
     - i. Reticulum cell
     - ii. Megakaryocyte.
   - (b) Of lymphoid origin
     - i. Reticulum cell.
     - ii. Lymphocyte.
2. *Hodgkin's disease is an inflammation*
   - (a) Of infectious origin.
   - (b) Of "toxic" origin.
   - (c) Of allergic origin.
3. *Hodgkin's disease is "midway between an inflammation and a neoplasm"*
4. *Hodgkin's disease is a metabolic abnormality*
   - (a) Due to hormonal imbalance.
   - (b) Due to other metabolic imbalance.
   - (c) Due to autonomic nervous system imbalance.
   - (d) Due to allergy.

1. NEOPLASIA

There is a large body of literature supporting the contention that Hodgkin's disease is a neoplasm. Arguments which are said to be in favor of a neoplastic etiology have been assembled as follows:

Evidence based on distribution.—The reported distribution of Hodgkin's disease in the United States is similar to that of neoplastic diseases as a group, and to heart disease and diabetes mellitus. The reporting ability of the states as measured by the recorded incidence of heart disease, diabetes mellitus and cancer of all types, in general parallels the recorded mortality of Hodgkin's disease (244).

Evidence based on clinical manifestations.

1. The course is that of a patient with a neoplasm (89, 90, 323, 543).
2. The cachexia seen in the advanced stages is of a type which is said to suggest malignant neoplasm (191, 543).
3. The disease invariably progresses to a fatal termination (90, 323, 543).
4. Sex ratios suggest a tumor (479).
5. The familial incidence of the disease suggests a tumor.
6. The types (clinical, roentgenologic and pathologic) of pulmonary involvement in Hodgkin's disease, lymphatic leukemia and lymphosarcoma are quite similar (150).
7. Hodgkin's disease like carcinoma has not been observed to attack or pass through a joint. Infections have no respect for joints and cartilage (273).
8. The distribution of Hodgkin's bone lesions is similar to that of carcinoma in that the same group of bones (those that are richest in marrow) are most frequently involved (200).
9. Hodgkin's disease behaves like a tumor in its reaction to radiation (323).
10. The symptoms, progressive asthenia, pyrexia, secondary anemia, and weight loss, which suggest an infection are due to loss of the protective function of the lymphoreticuloendothelial system (171).

Evidence based on laboratory findings.

1. No specific agent has been found (514, 523, 543).
2. Immunologic specificity has not been demonstrated (252, 543).

Evidence based on pathologic observations.

1. The microscopic appearance is that of a tumor (191, 543).
2. The disease shows local invasiveness with a tendency to break through the capsule (191, 194, 323, 474).
3. Hodgkin's disease has a predilection for special tissues (474).
4. Metastases and infiltrative tendencies are on a cellular basis (543).
5. Pleomorphism is seen in some true tumors, *e.g.* teratomas (171).
6. Giant cells resembling those of sarcoma are present (191).
7. Large cells with clear, budding or plasma cell-like nuclei suggest a tumor (34).
8. The presence of frequent and atypical mitosis and of amitotic division is highly suggestive of tumor (34, 543).

Evidence based on histopathologic findings.—Any rational approach to the neoplastic nature of Hodgkin's disease must define the proliferating cell type or types. Many consider Hodgkin's disease to be of reticulo-endothelial rather than lymphoid origin. It has been reported that red bone marrow is a very frequent site of the disease. "Tissue which is lymphoid but poor in reticulo-endothelial tissue shows involvement in Hodgkin's disease in only about 10% of cases. When the tissues are rich in reticulo-endothelial cells and poor in lymphatic follicles, they are commonly the site of Hodgkin's disease" (490). Richness in reticulo-endothelial tissue, however, has been considered by some authors to be a result of the disease rather than an element predisposing to the development of the disease.

Pullinger (424) and almost simultaneously Fraser and Mekie (171) have summarized the case for the reticulum cell origin of the disease. Normal reticulum cells retain in adult life multipotential capacities similar to those of embryonal mesoderm (364). Reticulum cells may produce lymphocytes, histiocytes, free macrophages, sinus-lining cells and fiber-bearing cells of various kinds; or they may undergo direct myeloid transformation according to Lang (316). The reticulum cell (424) is the proliferating cell of Hodgkin's disease; it is prominent, frequently multinucleate, shows vacuolization, karyolysis, unusual numbers of mitotic figures and may attain great size and lose its phagocytic ability. All other cellular manifestations which are recognized as characteristic of Hodgkin's disease are due to subsequent differentiation of the reticulum cell. These cells are found in connective tissue throughout the body, and thus the varied sites of development may be explained. The number of leukocytes found in the lesions does not usually reflect the number in the circulating blood; they lie in no rela-

tion to blood vessels. They have a local origin due to the myelopoietic activity of the reticulum cell.

Pullinger concludes, in line with the ideas developed in the course of her survey, that lymphadenoma is not a chronic inflammation. Resemblances between the two conditions are incidental due to the fact that the proliferating root cell is capable of differentiating into all the constituents that compose a granuloma and into granular leukocytes as well. Vascular changes, however, play no essential part, and cellular response does not follow an orderly sequence. Reticulum and collagen fibrils often appear earlier than granular leukocytes and do not represent a healing process. Early stages may be atypical and difficult to recognize because the various indicators (giant and free reticulum cells, fibrils and eosinophilic leukocytes) have not yet differentiated. Late stages look like healed inflammatory lesions only because in the course of time a great many indestructible fibrils have been produced. Necroses can be accounted for without assuming that a bacterial toxin causes them and the nodular arrangement is based upon underlying groups or islands of reacting syncytium.

van Rooyen (523), at the end of many years of study of Hodgkin's disease, concurred with the conclusions of Pullinger. van Rooyen, moreover, found that not only nodes altered by Hodgkin's disease but also leukocytes and other myeloid tissues gave rise to a positive Gordon test on occasion. "The presence of a common characteristic existing between the reticulum cell and the leukocyte may help to strengthen the views of those such as Pullinger and MacNalty who have postulated the local origin of granular leukocytes in Hodgkin's disease in contradiction to the general opinion that they are the result of colonization and deposition via the blood stream." Ross (443) states that Hodgkin's disease may be a true reticulosis due to hyperplasia of undifferentiated cells having unrestricted potency for differentiation.

Medlar (374) is in general sympathy with the unitarian theory of myelopoiesis. The parent cell of the lymphoblast or myeloblast may be the megakaryoblast. While agreeing that local myelopoiesis accounts for the cellular changes of Hodgkin's lesions, Medlar considers the reacting cell to be the megakaryocyte and that the "histopathology of Hodgkin's disease is a pleomorphic aggregation of cells which represent the developmental cycle of the megakaryocyte. It is not necessary to have fibrosis, eosinophilic or neutrophilic infiltration to establish the diagnosis." Medlar believes that the Sternberg-Reed cell, the ultimate histologic criterion, is a megakaryocyte. The finding of increased numbers and large sizes of platelets is offered as additional evidence in favor of this interpretation of the origin of the disease. Medlar and Sasano report an occurrence of a spontaneous Hodgkin's-like disease in a rabbit (376). Foci of erythro- and myelopoiesis were found in the involved organs. Medlar and Sasano conclude that the pathologic appearance of the lesions in the rabbit supports their suggestion that Hodgkin's disease is a malignancy of the bone marrow in which the megakaryocyte is primarily involved.

Mankin (354) reports that the essential tissue culture finding in Hodgkin's nodes is an alteration in the reticulo-endothelial cell. The work of Chlopin and his co-workers is quoted as indicating that normally the reticulo-endothelial cell is transformed into a fibroblast in tissue culture. Mankin, studying the tissue cultures of 20 cases of Hodgkin's disease, finds that the reticulum cells in the outgrowth from the explant have in a large degree lost the capacity to undergo the normal transformation into fibroblasts. These findings are compared to tissue culture studies of 8 normal lymph nodes (obtained from 8-month old foetuses) and several cases of tuberculous and lymphadenosis lymph nodes. Brief mention is made of the behavior of the Sternberg-Reed cell in tissue culture. It is stated that this cell can be recognized and identified in some cultures in the outgrowth 2 to 3 days after explantation of Hodgkin's tissue. No photographs or drawings of this finding are included in this paper which is otherwise profusely illustrated. Mankin after an extended discussion of the multinucleated giant cell as seen in Hodgkin's tissue cultures, concludes that these are a variety of foreign-body giant cell. Elaborate histologic studies of the transformation of reticulum cells into fibroblasts as seen in tissue cultures of non-Hodgkin's lymphoid tissue are presented. Emphasis is placed on the appearance of the tonofibrils in the elongated cells as the main criterion which identifies them as fibroblasts rather than reticulum cells. Mankin admits that there is often great difficulty in distinguishing between the reticulum cell and the early fibroblastic element. He does not believe, however, that this invalidates his general conclusions.

Motion picture tissue culture studies of the characteristic locomotion of the cells of Hodgkin's disease have suggested to M. R. Lewis (327) that the Sternberg-Reed cells are of myeloid origin rather than lymphoid or monocytic. These cells were compared with normal cells and "malignant cells from lymphosarcoma, monocytoma and myeloblastic sarcoma." Lewis found that "the cultures of glands with Hodgkin's disease showed a luxuriant out-

growth of giant stroma cells containing large single or multilobed granular nuclei with large nucleoli. Tripolar and bipolar mitotic figures with an increased number of chromosomes were present. Lymphocytes, Dorothy Reed cells and stellate macrophages grew out in the early cultures but within a few days were overgrown by stroma cells. The small Dorothy Reed cells migrated freely with writhing motion, some of them identical in size, shape and locomotion with the myeloblasts. The large Dorothy Reed cells were sluggish and resembled megakaryocytes in size, shape and motion, except that while many of the Dorothy Reed cells were multinucleated, their nuclei were not lobed and had heavier nuclear membrances and larger nucleoli than those of megakaryocytes. They were not phagocytic and did not move like normal macrophages, epithelioid or Langhans cells. Dorothy Reed cells differed from malignant lymphoblasts and monoblasts but resembled malignant myeloblasts, particularly those which multiply in the lymph nodes in certain cancerous lesions."

Comparison with other lymphomas.—Most of the proponents of the myeloid origin of the reacting cell consider Hodgkin's disease to be a form of leukemia rather than a true malignant tumor. Symmers (503) considers that myelogenous leukemia and Hodgkin's disease are fundamentally related: "they are probably different quantitative responses to the same type of provocative agent." Mills and Pritchard (384) refer to Hodgkin's disease as a reticulo-endothelial leukemia. Pullinger (424) says: "The condition is not a true malignant neoplasm, since infiltration and metastases do not occur... Lymphadenoma is the most closely allied to the leukemias, since like them it is essentially a progressive hyperplasia of one type of cell. But whereas lymphatic and myelogenous leukemia are proliferations of partially differentiated types, Hodgkin's lesions start in the root cell of hemopoietic tissue. Differentiation, partial or complete, then follows. As in the two other conditions, alterations in the cellular content of the blood may or may not accompany the process. The frequently reported simultaneous occurrence of lymphadenoma and leukemia suggests that the stimulus in both the disturbances is similar, or that myeloid or lymphoid cells of the former have invaded the blood stream and confused diagnosis. The sex incidence—predominant among males—is common to all these conditions."

Hickey (236) has characterized this type of thought in the following manner. "Hodgkin's disease is related by some authorities to the leukemias; they look upon the whole group as an overproduction of various bone marrow cell types with an upset of the arrangements of imports and exports by overproduction, ultimately tending to destroy the whole organism. Those who hold this view of neoplasm do not necessarily cling to the possibility of an original infection."

Winkelman and Moore (555) do not believe that lesions of Hodgkin's disease require a nidus of mesenchymal tissue before they can develop (3). King, discussing the same paper, "cannot understand how Hodgkin's disease can properly take root in the nerve tissue where there is an absence of reticulum cells and other fixed mesenchymal elements" except by the mechanism of cellular metastasis. This is a particularly pertinent point especially since the lesions which Winkelman and Moore describe present all the characteristics of blood-borne metastases. The work of Maximow may help in part to answer this objection since he indicated that reticulum cells are found in all connective tissues. It is significant in this regard, however, that cases similar to the one presented by Winkelman and Moore are rather rare; the rarity may be related to the fact that connective tissue is found in such meager quantities in brain tissue. Hodgkin's lesions of the central nervous system including those which occur by direct extension from the meninges and bones are uncommon.

Another group of investigators defends the neoplastic nature of Hodgkin's disease but considers the lesion to be lymphoblastic rather than myeloblastic in origin. Since the reticulum stem cell is considered by most of these authors to be the lymphoblast, the difference between the two groups appears to be neither very distinct nor very significant. Their chief point of difference is the belief that the reticulum stem cell undergoes abnormal lymphopoiesis rather than myelopoiesis. The similarity between the course of Hodgkin's disease and that of the lymphoblastomas has been noted by many authors (19, 56, 91, 131, 194). Of possible interest too, are the occasional reports of Hodgkin's disease which are said to be found with, before or after the development of one or the other of the lymphoblastomas.

Mycosis fungoides is included as one of the lymphoblastomas; most authors place it in this category although its lymphoblastomatous nature has been questioned (474, 538).

A series of cases in which there is either a transition from one type of lymphoma to another during the course of the disease or in which there is a combination of 2 or more types of lymphoma observed in the same patient has been gathered from the literature. MacCormac (343) 1 case; Fraser

and Mekie (171) 1 case; Warfield and Kristjanson (540) 1 case; Ginsburg (194) 1 case; Herbut, Miller and Erf (234) 6 cases; Wile and Stiles (550) 1 case; Jackson (261) 9 cases; Craver (98, 101) 3 cases; and Yamasaki (563) 2 cases.

A study of material in the Army Institute of Pathology by Custer and Bernhard (118) included 200 autopsies and 500 biopsies of Hodgkin's disease patients and 600 cases whose major diagnosis was lymphosarcoma, reticulum cell sarcoma, lymphatic leukemia, monocytic leukemia or follicular lymphoblastoma. These authors concluded that

1. Instead of there being 5 or more separate and distinct neoplasms of lymphoid tissue, there is one.

Table VII: Transitions and Combinations of Histologic Types

	With Transition		Without Transition		Pure types		Combined types		No. of cases
	No.	%	No.	%	No.	%	No.	%	
AUTOPSY SERIES									
With biopsy	54	39	84	61	26	19	112	81	138
Without biopsy					45	74	17	26	62
BIOPSY SERIES									
Sequential biopsies	21	31	48	69	16	23	53	77	69
Single biopsy					305	71	126	29	431

Table VIII: Type of Lesions Observed in Different Lymph Nodes or Organs of the Same Individual at Autopsy (129 cases)

Hodgkin's paragranuloma		x	x			x	x	x		
Hodgkin's granuloma	x	x	x	x	x				x	
Hodgkin's sarcoma	x		x	x	x	x	x	x	x	x
Lymphosarcoma					x	x				
Fibrosarcoma				x						
Follicular lymphoblastoma								x	x	x
No. of cases	90	13	13	4	3	2	1	1	1	1

2. This single tumor entity may adopt any one of at least 7 different histologic patterns.

3. These may occur singly or in combination in a given patient, or there may be a distinct transition from one type to another during the course of the patient's disease.

4. Two of these variants, Hodgkin's paragranuloma and Hodgkin's granuloma, are clearly inflammatory in nature, yet each may adopt the cellular characters and clinical behavior of a malignant tumor.

5. This malignant lymphoma may be a virus-induced tumor. Work is in progress to investigate the disease from this angle. (See Tables VII and VIII.)

Some authors assert that the histologic points of similarity between lymphosarcoma and Hodgkin's disease are many and that the difference between these conditions is one of degree rather than kind (88, 194, 419). Warthin (543) considered Hodgkin's disease, the lymphoblastomas and mycosis fungoides to be "genetically related." He studied 589 biopsied and/or autopsied cases and concluded that these conditions varied only in the "different degrees of differentiation and dedifferentiation, and the organ or tissue primarily involved. . .All three diseases take their origin from perivascular reticuloendothelium or the maternal lymphoblasts of lymphoid tissue." Sugarbaker and Craver (500) agree that the borderlines between them "remain rather shadowy at present." Kierland and Montgomery (291), who review the problem from the point of view of the dermatologist, come to a similar conclusion: "In our experience, not infrequently, cutaneous lesions of Hodgkin's disease may be characteristic of one or the other of the lymphoblastomas without being diagnostic as to type. . .Transitions from one type of lymphoblastoma to another occur, and these frequently are seen as transitions of mycosis fungoides to Hodgkin's disease and of Hodgkin's disease to lymphosarcoma." H. E. Miller (382) found other lymphoblastoma "almost impossible to distinguish from Hodgkin's disease."

While many argue that the lymphocytes are mechanically displaced by the destructive lesions of Hodgkin's disease, reticulum cell hyperplasia and fibrosis (171, 559), there is a possibility that the physiology of the lymphocyte may be altered in this disease. The work of Chambers, Cameron and Kopac (74) may be suggestive in this respect. Using tissue culture explant cells of diseased and control nodes, these authors conclude that "the overall difference in sensitivity of lymphoid cells from malignant and normal sources to tetraethyl- and tetramethyl-*o*-phenylenediamine is sufficiently pronounced to be significant" (74). It is entirely possible that these diseases have lymphotoxic effects that render the cells more susceptible to the action of the various chemicals which Chambers and associates used. The lymphocytes from nodes of lym-

phosarcoma and lymphatic leukemia were slightly more susceptible to the action of the chemicals than those of Hodgkin's disease.

Herbut, Miller and Erf (234), whose cases of Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma occurring in the same patient have been cited, consider that the 3 diseases arise "from a common stem cell—the reticulum cell" from which differentiation occurs in one direction or another according to the amount and type of stimulation present. "Combination of these diseases results when the specific stimulators are not uniformly distributed throughout the organs and when a temporary excess of one is followed by an excess of the other." The "stimulation" to which the authors refer is metabolic and will be discussed in another section of this review.

TABLE VIII (cont'd)

Combination of type lesions (*) observed in single lymph nodes (255 cases)

Hodgkin's paragranuloma		x	x	x				x		x		
Hodgkin's granuloma	x	x			x	x	x	x	x		x	
Hodgkin's sarcoma	x			x			x	x	x	x		x
Lymphosarcoma					x				x			
Fibrosarcoma						x	x					
Follicular lymphoblastoma			x							x	x	x
No. of cases	132	101	7	4	2	2	2	1	1	1	1	1

* Histologic patterns of significantly large fields, which if viewed alone would justify the diagnoses as listed.

2. INFLAMMATION

There is a large body of literature which upholds the theory that Hodgkin's disease is inflammatory rather than neoplastic in nature. Evidence which has been advanced against the neoplastic theory is as follows:

Evidence based on clinical manifestations.

1. The cachexia and anemia of the Hodgkin's patient is seen in many chronic infectious diseases, particularly the chronic infectious granulomas (81, 85, 113, 538).

2. The inevitably fatal course of Hodgkin's disease does not rule out infection; leprosy, torula histolytica and certain other granulomatous diseases are for the most part fatal (81, 538).

3. Occasional patients pursue a toxic and rapidly fatal course with elevation of temperature out of proportion to the amount of Hodgkin's tissue found at autopsy (445).

4. It is not uncommon for the lymph nodes to enlarge all over the body at the same time; this is not seen in tumors (81). Hodgkin's skin lesions may also become manifest all over the body at the same time (36, 245).

5. Remissions and exacerbations are suggestive of an infectious process (85, 474).

6. The presence of fever and sweats without identification of a secondary invader (81, 113, 538).

7. Tachycardia out of proportion to the rise in temperature (262).

8. Affected lymph nodes usually are those most easily infected through the skin or mucous membranes (85, 474).

9. Occasional acute cases resemble septicemias (85); acute episodes sometimes terminate the chronic case.

10. The occasional spontaneous and complete disappearance of enlarged lymph nodes without therapy and the peculiar relapsing type of fever, tachycardia, pain and changes in hematologic equilibrium are suggestive of a chronic infectious process (246).

Evidence based on laboratory findings.

1. Polymorphonuclear leukocytosis which becomes more pronounced with exacerbations and less pronounced with remissions (99, 245, 246).

2. The apparent similarity of the blood picture to that observed in tuberculosis rather than in neoplasm (559).

3. Elevated sedimentation rate is a consistent finding (245, 557).

Evidence based on pathologic observations.

1. Metastases are seen in numerous infectious diseases; dissemination may be due to the intracellular transfer of a living agent, possibly a virus (81).

2. The metastases in Hodgkin's disease do not necessarily kill the patient (81); he frequently dies because of toxemia which is out of all proportion to the apparent degree of dissemination of the disease.

3. Metastases of Hodgkin's disease to bone cause less pain and are more radiosensitive than those of metastatic carcinoma (200).

4. Invasive lesions are seen in many chronic infections, particularly infectious granulomas (81, 236, 538).

Evidence based on histopathologic findings.

1. The exceptional sarcomatous appearance of some Hodgkin's lesions is not conclusive since certain chemicals such as potassium iodide and zinc sulfate initiate a sequence of abnormal karyokinesis similar to that seen in neoplastic cells. In the latter case the cells later recover. Moreover, it is difficult to distinguish chronic inflammatory lesions from tumors (in the true neoplastic sense) in hemopoietic tissue (81).

2. The so-called metastatic lesions have the same histologic appearance and the same polymorphism of cells as do the so-called primary lesions (81, 503).

3. When serous surfaces are involved, the exudation is not like that seen in a neoplasm (113, 201).

4. The cells exhibit an orderly growth, as in a granuloma, rather than disorderly growth as in a neoplasm (311).

5. There is a polymorphism of cells in which no distinctive cell form appears to be most actively proliferating; there is usually no correlation between the degree of invasiveness and the histologic picture. The rapidly spreading lesions have a similar polymorphous appearance and the cell forms do not exhibit varying degrees of anaplasia (81, 431).

6. The behavior of explants of Hodgkin's tissue in tissue culture is unlike that of tumor tissue (212, 245, 311).

7. There are no neoplastic diseases in which so many apparently dissimilar histologic variations, united only by the presence of small numbers of one type of cell (the Hodgkin's cell) are classified under one name, and for which there are a coexistent number of diverse clinical syndromes and organic manifestations (245).

8. Hodgkin's lesions may be interpreted as an inflammatory hyperplasia of the lymphoid tissue with a polymorphous reaction of the mesenchymal cells; the giant cells are of inflammatory rather than neoplastic origin. The prominent fibrous tissue response is the attempt at healing which follows inflammation (81).

9. There is little new vessel formation, a common characteristic of chronic inflammatory lesions, especially infectious granulomas, but not of new growths (81).

Other evidence.—Krumbhaar (311) and Fabian (149) believe that Hodgkin's disease is an inflammatory condition; they agree, however, that well-proven cases have become sarcomatous with time. Except for these latter cases, "the characteristic picture of Hodgkin's disease can be harmonized only with a primary neoplastic theory if one assumes that it is an inflammatory response, of a type not known in connection with any other neoplasm, to an existing neoplasm whose presence in the tissue cannot be demonstrated." Craver (96) states that the occurrence of fever, rashes, eosinophilia, local and general distribution of lesions, unusual modes of extension and infiltration, frequent traces of the allergic phenomenon and frequent leukocytosis suggest an inflammatory rather than a truly neoplastic process, but at the same time feels that we cannot overlook other evidence in favor of a neoplastic nature. The French term *maladie de frontière* seems well chosen. Another author (244) writes: "It is the opinion of a majority of students of the subject that Hodgkin's granuloma appears to be a non-malignant process, probably of infectious origin. . .It is felt that a clinical and pathologic disease syndrome with a frequency distribution extending throughout the life span should not be considered in the same etiologic group with a presumably neoplastic disease syndrome such as Hodgkin's sarcoma."

There is additional evidence concerning the inflammatory theory of the disease. The work of Erxleben and Herken (146) is interesting in this regard. They reported that non-tumorous pathologic and normal tissue contained less than 2% of *d*-glutamic acid in the glutamic acid samples isolated from proteins (a) of normal and necrotic rabbit kidneys in which the necrosis was produced by the occlusion of blood vessels, (b) from livers of rabbits with diffuse hepatitis resulting from the injection of foreign protein, (c) from human miliary tuberculous lungs and (d) from the tissues of Hodgkin's disease in man. The total glutamic acid (5.8%) from proteins of a mediastinal lymph node of a pig with leukosis contained 2.4% of *d*-glutamic acid. Saranella virus myxoma proteins of rabbits contained 6.1% of glutamic acid 11.0% of which was *d*-glutamic acid. Erxleben concludes that the appearance of *d*-glutamic acid in more than normal quantities in tissue protein must be regarded as specific for tumors and not a widely distributed pathologic finding.

Beckton (26) finds Altmann granules in normal glandular structures, plasma cells, lymphocytes, endothelial cells and fibroblasts and in the same cells of inflammatory lesions. Simple proliferations of lymphoid tissue are said to possess the same number of granules as compared with normal tissue, but in nonmalignant tumors the granules are said to be less numerous. Malignant neoplastic cells, on the other hand, are devoid of granules. MacCormac (343), who considered Hodgkin's disease and my-

cosis fungoides to be variants of the same inflammatory condition, found Altmann granules in the lesions of mycosis fungoides in abundance.

Further indirect evidence in favor of the inflammatory nature of Hodgkin's disease is seen in the report of a case of uveitis presumably due to Hodgkin's disease. Kamellin (278) did not know whether the two conditions were caused by the same agent. Since non-traumatic uveitis is almost invariably associated with an infectious disease, notably one of the granulomas, tuberculosis or syphilis, this report is interesting. A case of demyelinization in the central nervous system without apparent cause in a patient with Hodgkin's disease has been attributed to the toxic action of "lymphogranulomatous tissue" (25).

Bersack (36) describes a case which is highly suggestive of infection. The patient, a white man, developed miliary skin lesions. The initial lesions were small erythematous areas about 0.5 cm. in diameter; these, observed over the entire body by the hundreds, soon became slightly raised, circumscribed and finally nodular. New crops of lesions were accompanied by a rise in temperature. Biopsy of the early skin lesions indicated a normal epidermis with minimal reaction consisting of endothelial and fibroblastic proliferation about vessels and an increase in the number of lymphocytes in the corium. Biopsy of the older skin lesions indicated typical Hodgkin's disease. At autopsy there was miliary Hodgkin's disease in the serous surfaces, lungs, mucosa of the respiratory tree, pericardium, spleen, testes and the capsule of the pancreas. The abdominal and pelvic nodes were involved by the process. Since "no malignant cells were found in the microscopic examination of the early skin nodules," Bersack considered that this finding favored the infectious nature of the disease. "The hematogenous dissemination must have been mediated through the humoral content of the blood. The only alternative would be to incriminate the few lymphocytes in the initial stage of a new focus. They might possibly be the vectors of the noxus... It might be worthwhile to attempt transmission experiments with blood derived from a patient who, as in the present instance, is exhibiting blood stream spread."

Experiments of Perk Lee Davis described by Hoster (246) are of great interest. Chest fluid was withdrawn from a terminal Hodgkin's patient with pulmonary and pleural lesions and injected intramuscularly into the donor and 2 other patients with advanced Hodgkin's disease. At the end of 48 to 72 hours, all 3 patients developed a generalized maculopapular rash with severe itching. Vesicles then became one of the features of the rash. Although the generalized rash began to disappear after 3 or 4 days, a few lesions in certain areas became large and appeared as nodular, vesicular or ulcerative tumefactions. Biopsy of these lesions revealed the typical histopathology of Hodgkin's disease; the lesions responded to roentgen therapy but not to chemotherapeutic agents. The patients pursued a rapid downhill course following inoculation, suggesting that their disease had been accelerated. A similar report of somewhat less widespread dissemination of skin lesions following roentgen therapy over an involved spleen suggests autoinoculation from a disrupted focus (246).

Those who affirm the inflammatory nature of the disease consider the reaction to be chiefly that of the monocyte-reticulum cell-histiocyte series. Thus Reed (431) says, "Microscopically, Hodgkin's presents a peculiar histological picture somewhat similar to a chronic inflammatory condition. . .consisting of proliferations of the endothelial (reticulum) and reticular cells." Potter (442), who re-studied the histology of Hodgkin's disease in 1935, came to a similar conclusion. McJunkin (370) working with tissue cultures thinks that the chief reacting cell of Hodgkin's disease "appears to be identical with the monocyte of the blood. The monocyte of the blood in turn is like the reticular cell of lymphoid tissue." McJunkin found that the Rous chick sarcoma cells reacted in tissue cultures like the blood monocytes. Their appearance was strikingly similar when stained supravitally with neutral red. Since the Rous sarcoma is caused by a cell-free filtrate, presumably a virus, this observation may be of interest.

Wiseman (559) studied the blood picture and concluded that "an infectious agent of low virulence, of non-pyogenic origin, which results in a pathologic alteration and hyperplasia of the reticulum cell-monocyte maturation cycle, allied on the one hand to the tubercle bacillus or on the other to monocytic leukemia, would best explain the cellular reaction produced in the blood by this disease." Wiseman did not consider the occasional conversions of Hodgkin's lesions to sarcoma to be in opposition to its inflammatory nature, "since the frequent association of chronic lesions with neoplasm is well-known."

Although many investigators uphold the theory of malignancy on the ground that Hodgkin's disease is very similar to other lymphoblastomas, others question this theory by pointing out the differences:

1. Although reticulum cell sarcoma and lymphosarcoma may be exceptions (96) the lymphoblasto-

mas are said to exhibit symmetrical lymph node involvement early; Hodgkin's disease in the early stages is characterized by unilateral involvement (367).

2. All varieties of lymphoid hyperplasia are found in mice. Leukemia, pseudoleukemia and lymphosarcoma, observed in mice, have distinctive anatomical and histologic features which suggest that they are fundamentally of similar nature. No lesion similar to Hodgkin's disease has been described in mice (473).

3. Hodgkin's disease, unlike lymphosarcoma and leukemia, has never been unequivocally identified in lower animals (311).

4. Findings concerning the relation between sex and prognosis are not similar in Hodgkin's disease and lymphosarcoma, a finding considered as additional evidence that the two conditions are not the same (145, 181).

5. The reaction of Hodgkin's disease to roentgen rays differs from that of leukemic and neoplastic diseases in general (163).

6. Examination of the spleen, when involved, invariably distinguishes between the lymphoblastoses and Hodgkin's disease; the 2 diseases are different (296).

7. Histologic study suggests that Hodgkin's disease, the group of sarcoma arising from reticuloendothelium and the group of leukemias and aleukemias represent 3 distinct entities (422).

8. Of 319 patients with Hodgkins' disease, only 2 cases with subcutaneous nodules were seen, and lesions of the mucous membranes were conspicuously absent. This is unlike lymphosarcoma, in which the reverse is true (200).

9. Interpretation of the blood picture suggests that Hodgkin's disease is not one of the lymphoid hyperplasias (559).

10. The distribution of the lesions of Hodgkin's disease corresponds to the distribution of reticuloendothelium; lymphosarcoma lesions correspond to the sites of lymphoid tissue (490).

11. Mycosis fungoides is not seen in children; Hodgkin's disease is not infrequently observed among the latter (470).

While some authors (81, 571) consider mycosis fungoides and Hodgkin's disease to be variants of the same disease, others believe that Hodgkin's disease and mycosis fungoides are separate. Markowitz (358) considers that "from a clinical point of view it is more plausible to accept infection as a greater probability than neoplasm in mycosis fungoides. Disappearance of original nodules and extension elsewhere is not characteristic of true malignancy. Nodules reach large size, but they too often disappear...(and this behavior)...cannot be called metastasis." Ormsby and Finnerud (405) point out the presence of features in mycosis fungoides not seen in Hodgkin's disease such as the relative paucity of large giant cells, the presence of major lesions in the skin rather than elsewhere and the presence of nuclear and protoplasmic detritus in regressing lesions. MacCormac (343) considers mycosis fungoides an inflammatory condition identical with Hodgkin's disease.

For the most part, students of Hodgkin's disease who uphold its inflammatory nature consider it to be an infection with an undiscovered bacterium or virus playing the etiologic role. There are others, however, who consider the inflammation of toxic origin. In this connection, Medlar and Sasano (375) say "The injury to the tissue to which Hodgkin's disease is a response may be non-infectious. Bacteria need not be the cause." The intraperitoneal injection of "lymphotoxic serum" by Flexner (157) in 1903 produced changes in the mesenteric lymph nodes of rabbits which he thought were like the earliest changes in Hodgkin's disease. Since Bunting (51) found no organisms, he was led to a "new conception of the disease." He concluded that a focus of infection may elaborate a toxin injurious to lymph nodes with "the lymph nodes acting as a barrier to the toxin, protecting the body cells from its action at the expense of the lymphocytes." Longcope (337) considered Pel-Ebstein fever, itching, pigmentation, skin ulcers, blood changes, weight loss and cachexia to be indicative of intoxication. Hodgkin's-like lesions are reported by Brandt (46) following treatment of experimental animals with tar for two years.

3. THE "COMBINED" VIEWS

It is apparent that the picture of Hodgkin's disease presents evidence "in favor of neoplasm on the one hand and in favor of inflammation on the other." One group of investigators (81, 102, 340, 358, 437, 470, 503, 538) attempts to reconcile the 2 hypotheses by considering Hodgkin's disease to be "midway between an inflammation and a neoplasm." Simmons and Benet (470) reported that Hodgkin's disease had no criteria by which it might be judged a neoplasm or an infection. Craver (102), however, offers a somewhat different interpretation of the combined view: "We look upon Hodgkin's disease as an inflammatory overreaction on the part of the lymph node structures to various stimuli, a process which, once established, goes on of its own momentum and may even progress to a true sarcoma." This is not unlike a previously stated hypothesis concerning Hodgkin's

disease made by Piney that "lymphogranulomatous tissue is a mere mark of severe injury of the reticuloendothelium through different causes." In a similar vein it is Desjardins' opinion that all lymphomas including Hodgkin's disease are a response of the hereditarily predisposed lymphoid system to chronic infection of any kind. Desjardins considers the established lesion to be a neoplasm (128).

The division of the disease into paragranuloma, granuloma and sarcoma by Jackson and Parker (262) in a sense combines the inflammatory and neoplastic views but fails to clarify the question of etiology. The authors consider that paragranuloma has no resemblance to a true tumor and is a true inflammatory lesion. The granuloma presents characteristics of both but is thought to be inflammatory and to bear a relation to paragranuloma similar to the relation of fibrocaseous tuberculosis to the primary tubercle. Hodgkin's sarcoma on the other hand is considered to be a true neoplasm. The paragranulomatous frequently progresses to the granulomatous form and the latter in turn occasionally develops into the sarcomatous. At an unknown point along this line of progression the inflammation takes on neoplastic characteristics. In explanation, Jackson and Parker refer to the suggestion of Chevallier and Bernard that the lesions of Hodgkin's disease are an "inflammatory reaction due to a virus which later changes into a blastoma."

The infectious and neoplastic theories are combined in the concept of Hodgkin's disease as a virus tumor analogous to the Rous sarcoma and avian lymphomatosis (243, 370). McJunkin (370) reported a similarity in the appearance of Hodgkin's granuloma cells and Rous sarcoma cells stained supravitally. Custer and Bernhard (118) consider the malignant lymphomas (one of whose variants is Hodgkin's disease) to be a virus induced tumor disease syndrome.

4. METABOLIC DISEASE

The early hypothesis that Hodgkin's disease may be a manifestation of constitutional disturbance has been restated in the modern literature. Cooper (93) has postulated the susceptible constitutional type as the young adult male with a relatively "broad type of build," wide face and fair hair. The work of Gemmell (190) suggests that the variations in sex incidence may be on a hormonal basis and that the disease in women is more likely to occur when there is decreased ovarian function.

Epstein (145) reported similar differences in susceptibility of the sexes and added that mortality from the disease in women seems to be greatest during periods when the physiologic processes are most like that of the male. Epstein, however, did not believe that the disturbance was primarily in the ovary since he treated a case with ovarian extract without success. "The effect... of the menstrual function on other glands may in turn influence the course of the disease." Epstein added, "functional differences in no way related to the endocrine system may afford a protective factor in women." Epstein found the rapidity of progression of the disease among females to be highest during the first 10 years of life. Furthermore, if the difference between susceptibility and resistance to the disease is on a sex hormone basis, the incidence and rate of progress of the disease in male and female children should be similar. Since this is not the case, it is probable that other factors must be implicated. Whatever the true interpretation may be, sex differences in all the lymphoblastomas remain a very prominent finding.

Hormones, other than those directly concerned with sex, are under suspicion in this disease. The following relations between the lymphoid tissues and endocrine states may be cited as examples:

1. Lymphoid hyperplasia is related to hyperactivity of the thyroid gland (94, 383).
2. Hypertrophy of lymph nodes is seen in adrenalectomized animals (111).
3. Injection of anterior pituitary adrenotropic hormone in mice is said to result in lymphopenia and absolute leukocytosis (137).
4. Castration in mice causes lymphoid hyperplasia (461).

Miller and Turner (383) find substances in human urine obtained from patients with leukemia, which they believe are "lymphoid" or "myeloid" according to the reaction they produce in animals. The myeloid substance is thought to stimulate myelopoiesis. "The maturation of myeloid cells is brought about by the action of the lymphoid substance which inhibits their proliferation and hence allows them to mature." The lymphoid substance brings about lymphoid proliferation and the myeloid substance is required for lymphoid maturation. The leukogenic substances are found in the acid fraction of hydrolyzed urine extract. One factor can be separated from the other. The myeloid substance is a keto acid and the lymphoid an hydroxy acid. The myeloid substance can be changed to the lymphoid by reduction and the lymphoid to the myeloid by oxidation. Miller and Turner explain the development of leukemia as follows: lymphatic leukemia ensues when the lymphoid substance is present in excess or the myloid substance is present in subnormal concentration; the develop-

ment of myeloid leukemia involves an excess of the myeloid, or deficiency of the lymphoid substance.

The myeloid reaction (produced by injecting a urine fraction from patients with chronic myeloid leukemia into guinea pigs) is described as follows:

1. Hyperplasia of the myeloid elements of bone marrow.
2. Frequent enlargement of the spleen with more or less myeloid metaplasia (including erythroid, leukoplastic, and platelet-forming elements).
3. Enlargement of the liver with metaplasia and enlargement of the adrenals.

The lymphoid reaction seen after the injection of a urine fraction obtained from patients with chronic lymphatic leukemia presents the following findings:

1. Hyperplasia of all the lymphoid elements.
2. Occasional disruption of the architecture with invasion of the capsule by new cells.
3. The adrenal medulla becomes the site of lymphoid hyperplasia when it is involved.
4. Kidneys and lungs often show lymphoid hyperplasia.

The so-called "Hodgkin's disease reaction" is observed after the injection of a urine fraction from patients with Hodgkin's disease, after the injection of the combination of myeloid and lymphoid fractions obtained from leukemic urines or after the injection of the fraction obtained from monocytic leukemia urine. The changes are described as follows:

1. Resembles the lymphoid reaction but lymph nodes attain larger size.
2. There is reticulum cell hyperplasia, many eosinophils and beginning pleomorphism.
3. Mitotic figures are often seen.
4. Giant cells are not uncommon but no Sternberg-Reed cells are found.
5. Kidney changes are very common.

The substances which produce the "myeloid" and "lymphoid" reactions can also be extracted from normal beef liver and, normal human urine; the hypothesis is that these sources contain equal amounts of the two factors. In chronic leukemia there is an excess of the myeloid or lymphoid substance and a normal amount of opposing substance, "the cells remaining mature until the maturing substance is exhausted." There is a deficiency or absence of the maturing substance in acute leukemias. In Hodgkin's disease (and monocytic leukemia) both substances are found in equal and greater than normal amounts in the urine of affected patients. No explanation of this phenomenon is given and the authors do not attempt to explain how interaction of excess myeloid and excess lymphoid substances produces the "Hodgkin's-like" reaction.

Langer (317) relates the production of leukemias and lymphoblastomas, among which he includes Hodgkin's disease, to overexcitation of the leukopoietic tissues by the vegetative nervous system. He suggests that nervousness, irritability, restlessness and increase in basal metabolic rate in these patients are indicative of autonomic imbalance. Herpes zoster is considered to be a regional manifestation of the general nervous disturbance that is present, Langer believes that the beneficial effect of sunlight in leukemia may be explained by a reflex through the ganglia and vegetative nervous center. He points to the fact that irradiation over the sympathetic ganglia results in reduction of distant Hodgkin's tumors in more than 50% of cases and to the fact that there is a better response to direct irradiation following exposure of the paravertebral ganglia to x-rays. Disturbance of the autonomic nervous system is also implicated by Chevallier and Bernard (81) who report that the disease occurs more frequently and is more rapidly fatal in the "megalosplanchnic" (hypersympathetic or sympathicotonic) individual than in the microsplanchnic. However, in viewing this statement critically, proof that a patient was "megalosplanchnic" before Hodgkin's disease developed is difficult to establish if the patient was not observed by the investigator at that time.

5. SPONTANEOUS DISEASE IN ANIMALS

Studies concerning the etiology of Hodgkin's disease are made more difficult by the fact that no strain of animals in which Hodgkin's disease occurs spontaneously or can be produced experimentally is available. Spontaneous disease in animals, if it occurs, is rare since there are few reports in the literature (311).

Feldman (152a) says: "Although Hodgkin's disease no doubt exists as a separate disease of man . . .I seriously doubt its existence in lower animals. I have never encountered a case in a study of approximately 600 neoplasms from animals. . .My experience is similar to that of Fox. . .he failed to see any case resembling that of Hodgkin's disease of man in the thousands of captive wild animals under his observation."

The conclusion of this article appears in the February issue.